Classification of IgA nephropathy

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IgA nephropathy is defined by the presence of dominant or co-dominant mesangial deposits of IgA. Lupus glomerulonephritis with extensive IgA is excluded. It may be primary, part of the syndrome of Henoch-Schönlein purpura, or secondary to a number of other extra-renal conditions, particularly diseases of the liver or gastrointestinal tract. It is the most prevalent form of glomerulonephritis worldwide. Frequency of biopsy diagnosis depends both on policies for screening of asymptomatic individuals and criteria for renal biopsy particularly in patients with isolated haematuria.

By light microscopy the glomeruli may show any of the morphologic manifestations of immune complex glomerulonephritis from normal, through mesangial proliferation, endocapillary proliferation and segmental necrosis to severe crescentic glomerulonephritis. Segmental proliferation and segmental scars are common. Glomerular scarring is associated with tubular atrophy and interstitial fibrosis.

By immunohistochemistry IgA is the sole immunoglobulin in 26% of biopsies. 25% have IgA, IgG and IgM. C3 is present in 95%. C1q is present in only 12% of biopsies and if prominent should raise the possibility of SLE.

There is a significant risk of progression to end stage renal disease in IgA with renal survival at 10 years ranging from 65 to 85% depending on geographical area. This almost certainly reflects, in part, different policies for performing renal biopsies (1). Many studies have considered the factors, both clinical and pathological, that predict outcome in IgA nephropathy and this is well summarised by Coppo and D'Amico (2). In addition several classification systems have been proposed for stratifying the risk of progression in IgA nephropathy. Classification serves a number of functions including

- Prediction of clinical course
- Guiding selection of therapy and predict response
- Guiding and stratifying inclusion in clinical trials
- Providing insights into pathophysiology that may help with design of therapy in future

However a study by Catrann’s group in 2001 (3) suggested that histological classification did not add anything to the use of clinical parameters in prediction of outcome. On this background the Renal Pathology Society and the International IgA Nephropathy Network set up an international group of pathologists to produce an evidence based international consensus classification of IgA nephropathy which has now been published as the Oxford Classification (4;5)
The Oxford Classification

The approach adopted in the Oxford classification was:

- Define the histological lesions
- Test the reproducibility of pathologists in recognising and scoring these lesions
- Collect evidence from a clinicopathological study on relationship of lesions and outcome
- Then propose a classification

Histological lesions were first defined by consensus at an initial Oxford meeting in 2005. This was followed by provisional analysis of the first 40 cases, to identify areas of high inter-observer variation. In order to improve reproducibility, definitions were then refined at a meeting of pathologists in Atlanta in 2006. Once satisfactory definitions of the pathological lesions were achieved, slides from 256 biopsies from adults and children were circulated for scoring for a large number of histological variables. The variables to be analysed in the clinicopathological analysis were then selected on the basis of reproducibility and independence from other lesions. Final analysis of the clinical follow-up data showed that there were 4 lesions that were independently predictive of clinical outcome:

1. Mesangial cellularity score
2. Segmental glomerulosclerosis/adhesion
3. Endocapillary hypercellularity (segmental or global)
4. Tubular atrophy/interstitial fibrosis

Furthermore, these variables could be divided into categories without significantly losing prognostic information as follows:

1. Mesangial hypercellularity score - 0.5 (corresponds to >50% of glomeruli with mesangial hypercellularity) (M0 or M1)
2. Endocapillary hypercellularity – present/absent (E0 or E1)
3. Segmental sclerosis – present/absent (S0 or S1)
4. Tubular atrophy 0-25%, 26-50%, >50% (T0, T1 or T2)

It was recommended that in the Oxford classification each of these variables should be reported separately. Thus an example of the bottom line of a report would be
There is IgA nephropathy showing diffuse mesangial proliferation with focal segmental sclerosis and moderate chronic tubulointerstitial damage (M1,E0,S1,T1)

Since the publication of the classification we have carried out a separate analysis of the 59 biopsies from children in the initial cohort and shown that the same features are predictive as in adults (6). Ian Roberts has also analysed the available immunohistochemical results from the biopsies and shown that capillary wall IgA associated with greater mesangial cellularity and more endocapillary proliferation. The presence of IgG is also associated with more endocapillary proliferation. However the immunohistochemical data do not add to the information that can be derived from the light microscopic features.

**Future work**

The Oxford classification is a unique example of an evidence based consensus classification of renal disease. However, it is only based on a single cohort of patients and validation from other studies is needed. A number of these are in progress but as yet none is published.

The primary aim of the classification was to assess histological features that predicted outcome. However, a more interesting question is which features are able to predict response to therapy. The Oxford study is unable to provide information on this although it is interesting that in patients who were treated with immunosuppressive agents endocapillary hypercellularity is less strongly associated with declining renal function suggesting it may be a lesion that responds to treatment.

Future studies should also consider using other tissue markers such as immunohistochemistry for inflammatory cell subsets and for complement components.

**References**


