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THE OXFORD CLASSIFICATION OF IgA NEPHROPATHY: SINGLE CENTRE EXPERIENCE

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A b s t r a c t: The Oxford classification for the pathological classification of a glomerular disease in IgA nephropathy was established and published in 2009. Four of the pathological variables: 1) mesangial hypercellularity score, 2) segmental glomerulosclerosis, 3) endocapillary hypercellularity and 4) tubular atrophy/interstital fibrosis were presented as having value in predicting renal outcome in this glomerular disease. These features were recommended to be taken into account for predicting the outcome. In our study, we correlated these four variables with the outcome of the disease in 40 adult patients with IgA nephropathy. Standard histopathologic procedure was used to determine four variables as 0/1. The results were compared with renal outcome, clinical data were obtained from the out-patient files of the patients. The whole follow-up period was 3–27 years. The average survival of the whole group was 10.8 ± 7.47 years (M ± SD). Mesangial hypercellularity was confirmed to be associated with the renal outcome ($p = 0.047$), as well as glomerular sclerosis ($p = 0.009$), endocapillary hypercellularity ($p = 0.001$) and tubular atrophy/interstitial fibrosis ($p = 0.045$). When we analysed only patients with a severe form of the disease (nephrotic syndrome; patients treated with immunosuppression), the survival of the patients was associated only with the degree of tubulointerstitial changes ($p = 0.018$). Analysing separately patients with mild clinical form, we found only a predictive value of segmental glomerulosclerosis on renal survival.

Key words: IgA nephropathy, glomerulonephritis, tubulointerstital changes, renal failure.

Introduction

The diagnosis of IgA nephropathy, the commonest glomerular disease worldwide, is defined by the presence of mesangial IgA-dominant immune deposits within glomeruli in the absence of systemic disorders [1, 2, 3, 4, 6]. But this criterion is the reason for a wide range of histological changes in IgA nephropathy (IgAN) and a different outcome of the renal disease [1, 5, 7]. Biopsy appearances may range from normal glomeruli by optical microscopy to severe crescentic glomerulonephritis, or sclerosing glomerulonephritis. Some biopsies present dominant diffuse mesangial proliferation and the others focal proliferative changes with different degrees of tubulointerstitial changes.

Thus many authors in the past tried to make a useful classification, comparing the histopathological findings with clinical features and the outcome of the disease [7, 8, 9, 10]. None has achieved widespread acceptance, because of a lack of definitions, and inclusion of both active and chronic lesions in the definition of single categories. Each of these classifications has been developed from expert opinion, each has strengths and limitations in predicting prognosis. There is continuing discussion as to whether pathological features seen on renal biopsy contribute additional prognostic information in addition to the clinical features.

The aim of the new Oxford classification [11, 12, 13] was to identify specific pathological features that can predict risk of progression of renal disease in IgAN. Four of the pathological variables were identified as having an independent value in predicting renal outcome: 1) the mesangial hypercellularity score, 2) segmental glomerulosclerosis, 3) endocapillary hypercellularity, and 4) tubular atrophy/interstitial fibrosis. These features were recommended to be taken into account for predicting an outcome independent of the clinical features both at the time of presentation and during follow-up.

The aim of our study was to compare the value of these four pathologic variables and outcome of the disease in our patients with IgA nephropathy.

Patients and Methods

We studied a retrospective cohort with biopsy-proven IgAN at the University Nephrology Department, Skopje, which covers renal biopsy diagnosis in all areas of R. Macedonia (about 2,000,000 people). 98 adult patients were classified as having IgAN during the years 1976–2006. The diagnosis of IgAN was based on the demonstration by direct immunofluorescence of mesangial IgA deposition in isolation or as the predominant immunoglobulin and the lack of clinical or serological evidence of systemic lupus eryhtematosus, Henoch-Schoenlein purpura, or liver disease. Renal biopsies were processed for light and im-

munofluorescent micoscopy using standard methodologies previously descrybed. Electron microscopy was performed in 6% of the patients, and semi-thin sections in about 70%.

Selection of the patients

40 adult patients (25 male, 15 female, > 15 years) were selected for the study, patients with more than 10 glomeruli at optical microscopy and with a follow-up of more than 3 years. Clinical data at the onset and during follow-up were obtained from the in-patient and out-patient files of the patients.

Classification (Oxford)

We used four pathological variables proposed by the Oxford Classification as it is presented in Table 1.

Table 1 – Табела 1

Definitions of pathological variables used in the classification of IgAN
Дефиниции на патолошките варијабли користени во класификацијата ИгАН

Variable	Definition	Score
Mesangial hypercellularity	The score is the mean score for all glomeruli	M0 = < 0.5 M1 > 0.5
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft	S0 – absent S1 – present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina	E0 – absent E1– present
Tubular atrophy/interstital fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0–25% – T0 26–50% – T1 > 50% – T2

Statistics

Statistics included Student's T test, Spearman's test and Mann-Whitney U Wilcoxon test to compare histological scoring and duration of follow-up without end-stage renal disease. Histopathological score and survival were compared in three different ways: 1) in all 40 patients, independently of clinical signs

and treatment; 2) 12 patients with nephrotic syndrome (defined as proteinuria > 3g/daily) and immunosuppression were analysed separately, and 3) the other 28 patients, with mild clinical features and without immunosuppression, were also analysed separately. The Kaplan-Mayer test was performed to determine the survival of the patients.

Results

Results of the whole group (40 patients)

The average survival of the whole group was 10.8 ± 7.47 years (M ± SD). 20/40 (50%) of the patients experienced end-stage renal disease after a period of 3–12 years. Pathological variables and follow-up of the patients is presented at Table 2. Mesangial hypercellularity was confirmed to be associated with the renal outcome ($p = 0.047$), as well as glomerular sclerosis ($p = 0.009$), endocapillary hypercellularity ($p = 0.001$) and tubular atrophy/interstitial fibrosis ($p = 0.045$).

Table 2 – Табела 2

Pathological variables proposed by Oxford classification and follow-up of the patients
Патолошки варијабли предложени со класификацијата Oxford и следење на пациентите

Patient	M	S	E	T	Period of follow-up	ESRD	Group
1.	1	0	0	0	27 years	/	I
2.	0	0	0	0	23 years	/	I
3.	1	1	0	0	4 years	after 4 years	I
4.	0	0	0	0	20 years	/	I
5.	0	0	0	0	20 years	/	I
6.	1	0	0	0	10 years	after 10 years	I
7.	1	1	0	0	4 years	after 4 years	I
8.	1	1	0	1	3 years	after 3 years	I
9.	1	0	0	0	6 years	after 6 years	I
10.	1	1	0	0	10 years	after 10 years	I
11.	1	0	0	0	23 years	/	I
12.	0	0	0	0	20 years	/	I
13.	0	0	0	0	10 years	/	I
14.	1	0	1	0	5 years	after 5 years	I
15.	1	1	0	0	6 years	after 6 years	I

Patient	M	S	E	T	Period of follow-up	ESRD	Group
16.	0	0	1	0	10 years	/	I
17.	0	0	0	0	12 years	after 12 years	I
18.	0	0	0	0	30 years	/	I
19.	1	1	0	0	15 years	/	I
20.	1	1	0	0	4 years	after 4 years	I
21.	1	1	0	0	3 years	after 3 years	I
22.	1	0	0	0	17 years	/	I
23.	0	0	0	0	10 years	/	I
24.	0	0	0	0	10 years	/	I
25.	1	0	1	0	8 years	after 8 years	I
26.	1	0	0	0	10 years	/	I
27.	0	1	0	0	6 years	after 6 years	I
28.	1	1	0	0	27 years	/	I
29.	1	0	0	0	10 years	after 10 years	II
30.	1	1	1	0	4 years	after 4 years	II
31.	1	1	0	1	3 years	after 3 years	II
32.	1	1	1	0	10 years	after 10 years	II
33.	1	1	1	1	4 years	after 4 years	II
34.	0	1	0	0	6 years	/	II
35.	1	1	1	1	5 years	after 5 years	II
36.	1	0	1	0	6 years	/	II
37.	0	0	1	0	7 years	/	II
38.	1	0	0	0	6 years	after 6 years	II
39.	1	1	0	0	12 years	/	II
40.	1	0	1	0	6 years	/	II

M – mesangial hypercellularity
S – segmental glomerulosclerosis
E – endocapillary hypercellularity
T – tubular atrophy/interstitial fibrosis
Group I – patients without nephrotic syndrome
Group II – patients with nephrotic syndrome

Results of Group I patients (without nephrotic syndrome or specific treatment)

This group consisted of 28 patients with normal renal function, without hypertension and nephrotic syndrome at presentation. 13/28 (46.1%) of these patients, in contrast with mild clinical features at presentation, presented end-stage renal disease during follow-up. Mesangial hypercellularity did not correlate with renal survival in this separated group of patients ($p = 0.053$ Mann Whitney, $p = 0.49$ Spearman test). Segmental glomerulosclerosis significantly correlated with the outcome of the disease ($p = 0.007$ Mann Whitney, $p = 0.006$ Spearman test).

Endocapillary hypercellularity (p = 0.351, p = 0.32) as well as tubular atrophy/interstitial fibrosis (p = 0.071, p = 0.105) did not correlated with the renal outcome.

Results of Group II patients (with nephrotic syndrome and immunosuppressive treatment)

Group II consisted of 12 patients with severe clinical features at presentation and necessary immunosuppression. 7/12 (58.3%) developed terminal phase of chronic renal failure during follow-up. Renal survival was not associated with mesangial hypercellularity (Mann-Whitney p = 0.606, Spearman test p = 0.607); with glomerular sclerosis (p = 0.343, p = 0.302) and endocapillary hypercellularity (p = 0.53; p = 0.533), but it was associated with the degree of chronic tubulointerstitial changes (p = 0018, p = 0.016).

It can be seen that there was noted significant difference in survival between these two groups of patients. Glomerular sclerosis was a poor prognostic pathologic variable in the patients without nephrotic syndrome, and tubulointerstitial changes in ones with nephrotic syndrome.

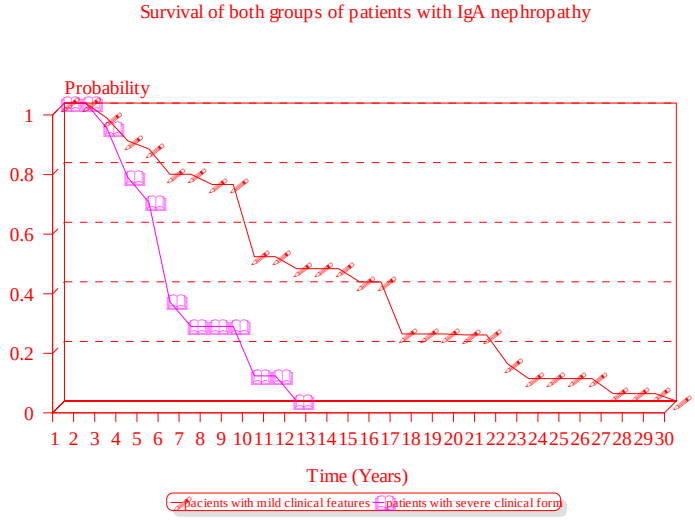

Figure 1 – The percentage of renal death in two groups of patients was similar (46,1%, Group I, and 58,3% in Group II), but renal survival (Kaplan-Mayer) was significantly better in Group I patients, with a probability of surviving for 30 years after renal biopsy, in contrast with Group II patients whose survival was estimated at 12.5 years
Слика 2 – Процентот на ренална смрт во двете групи на пациенти беше слична (46,1%, I група и 58,3% кај група II), но реналното преживување (Kaplan-Mayer) беше сигнификантно подобро кај пациентите од група I, со веројатност од преживување од 30 години по реналната биопсија, наспроти пациентите од група II чиешто преживување беше одредено на 12,5 години

Discussion

Many authors have tried to correlate clinical signs and histological features in IgA nephropathy [7, 8, 9, 10, 14, 15, 16]. Gross haematuria was frequently associated with mild glomerular lesions and a favourable clinical course; on the other hand, the presence of heavy proteinuria at the onset was frequently associated with severe histology and progressive renal disease. Severe histology was also associated with already decreased renal function and/or hypertension at the time of biopsy. Many authors believe that the histologic type of glomerular lesions appears to be the best predictive index in IgAN. The following factors were regarded as histological parameters of progressive damage in IgAN: severe mesangial proliferation, frequent sclerotic glomeruli, crescents, a higher proportion of glomerular adhesions, vascular sclerosis and marked interstitial fibrosis [8, 9, 14]. They are all causally correlated with each other in portending a poor prognosis.

Several histologic grading systems have been used in the past [8, 17, 18]. These pathological systems used to classify renal lesions in IgAN, can be divided into two groups: lumped and split. The lumped systems assess the overall severity of histological lesions, found in glomerular, tubular, interstitial and arteriolar compartments, as in the widely-used classification of Lee and Haas [8, 18]. The split systems use semiquantitative severity grading of lesions in each of the four compartments and permit the elaboration of a global or aggregate score for each compartment.

Lesions of focal and segmental hyalinosis and sclerosis were described as very specific for progression and so in our previous report we measured the sclerotic glomerular area and combined it with the semiquantitative score of the tubulointerstital changes in order to predict the progression (19).

In general, the agreement among the various classifications is only reached when considering renal disease already pogressed to sclerosis.

The new Oxford classification (11, 12, 13) documented by univariate and multivariate analysis that the following lesions resulted as independently predictive of clinical outcome: mesangial hypercellularity score, endocapillary hypercellularity, segmental glomerulosclerosis and tubular atrophy/interstital fibrosis. Necrotizing and crescentic lesions were not evaluated because of their rarity. Our results taking into consideration only these four histological variables presented the same results, a higher total score – a more progressive disease. Our group consisted of 40 patients of different ages, different clinical presentations and different treatment depending on the presence of nephrotic syndrome, and these four variables proposed by the Oxford classification were important for the outcome of the disease.

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REFERENCES

1. Clarkson A.R., Seymour A.E., Thompson A.J., Haynes W.D.G., Chan Y.L. and Jackson B. (1977): IgA nephropathy: a syndrome of uniform morphology, diverse clinical features and uncertain prognosis. *Clin Nephrol;* 8: 459–471.

2. Katz A., Underdown B.J., Minta J.O. and Lepow I.H. (1977): IgA nephritis unassociated with systemic disease. *Am Heart J;* 93: 670–671.

3. Berger J. and Hinglais N. (1968): Les dépôts intercapillaries d'IgA-IgG. *J Urol Néphrol;* 74: 694–695.

4. Druet P., Bariety J., Bernard D. and Lagrue G. (1970): Les glomérulopathies primitives à dépôts mésangiaux d'IgA et d'IgG. Etude clinique et morphologique de 52 cas. *Presse méd;* 78: 583–587.

5. Hyman L.R., Wagnild J.P., Beirne G.J. and Burkholder P.M. (1973): Immunoglobulin A distribution in glomerular disease: analysis of immunofluorescence localization and pathogenic significance. *Kidney Int;* 3: 397–408.

6. Polenakovic M., Dzikova S., Grcevska L., Polenakovic B. IgA nephropathy – Clinical and immunological examination, First Scientific Meeting of Yugoslav Nephrologists, Struga, 26–28 September 1977, *Proceedings*, Dokumenta e/12, Beograd, Galenika: 361–75.

7. Boyce H.N., Holdsworth S.R., Thomson N.M. and Atkins D.C. (1986): Clinicopathological associations in mesangial IgA nephropathy. *Nephron;* 6: 246–252.

8. Lee H.S., Koh H.I., Lee H.B. and Park H.C. (1987): IgA nephopathy in Korea: a morphological and clinical study. *Clin Nephrol;* 27: 131–140.

9. Packham D.K., Yan H.D., Hewitson T.D., Nicholls K.M., Fairley K.F., Kincaid-Smith P. and Becker G.J. (1996): The significance of focal and segmental hyalinosis and sclerosis (FSHS) and nephrotic range proteinuria in IgA nephropathy. *Clin Nephrol;* 46: 225–229.

10. Wakai K., Kawamura T., Matsuo S., Hotta N. and Ohno Y. (1999): Risk factors for IgA nephropathy: A case-control study in Japan. *Am J Kid Dis;* 33: 738–745.

11. Roberts I.S.D. *et al*. (A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society) (2009): The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int*, 76: 546–556.

12. Cattran D. *et al*. (2009): The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int;* 76: 534–545.

13. Coppo R., Cattran D., Roiberts I.S.D., Troyanov S., Camilla R., Cook T. and Feehally J. (2010): The new Oxford clinico-ptahological classification of IgA nephropathy. *Prilozi, Sec Biol Med, MASA;* 31: 1–8.

14. Choi S., Lee D., Jeong K.H., Moon J.Y., Lee S.H., Lee T.W. and Ihm C.G. (2009): Prognostic relevance of clinical and histological features in IgA nephropathy treated with steroid and angiotensin receptor blockers. *Clin Nephrol;* 72: 353–359.

15. Tsuboi N., Kawamura T., Koike K. *et al.* (2010): Glomerular density in renal biopsy specimens predicts the long-term prognosis of IgA nephropathy. *Clin J Am Soc Nephrol;* 5: 39–44.

16. Walsh M., Sar A., Lee D., Yilmaz S., Benediktsson H., Manns B. and Hemmelgarn B. (2010): Histopathologic features aid in predicting risk for progression of IgA nephropathy. *Clin J Am Soc Nephrol;* 5: 42–430.

17. Churg J., Sobin L.H. (1982): Renal Disease. Classification and Atlas of Glomerular Disease, Tokyo, Igaku-Shoin.

18. Haas M. (1997): Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. *Am J Kid Dis;* 29: 829–842.

19. Grcevska L. and Polenakovic M. (2000): Glomerular sclerotic area and tubulointerstitial changes: Prognostic significance in IgA nephropathy. *Nephron;* 86: 95–96.

Резиме

ОКСФОРД КЛАСИФИКАЦИЈА НА ИгА НЕФРОПАТИЈА: ИСКУСТВО НА ЕДЕН ЦЕНТАР

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Апстракт: Оксфорд класификацијата на патолошкото класифицирање на реналната болест кај ИгА нефропатијата беше поставена и објавена во 2009 година. Четирите патолошки варијабли: 1) степенот на мезангијална хиперцелуларност; 2) сегментната гломерулосклероза; 3) ендокапиларната хиперцелуларност и 4) тубуларна атрофија/интерстициелна фиброза, беше покажано дека се значајни за предвидување на исходот на реналното зафаќање кај ова гломеруларно заболување. Беше препорачано овие

карактеристики да бидат земени во предвид при предвидување на исходот на болеста. Во нашата студија ние ги корелиравме овие четири варијабли со исходот на болеста кај 40 адултни пациенти со ИгА нефропатија. Стандардна хистопатолошка процедура беше употребена овие четири варијабли да се одредат како 0/1. Резултатите беа компарирани со реналниот исход, клиничките податоци беа добиени од амбулантските истории на пациентите. Вкупниот период на следење изнесуваше 3–27 години. Средното преживување за целата група изнесуваше 10,8 ± 7,47 (М ± СД) години. Беше потврдено дека мезангијалната хиперцелуларност беше асоцирана со реналниот исход (п = 0,047), како и гломеруларната склероза (п = 0,009), ендокапиларната хиперцелуларност (п = 0,001) и тубуларната атрофија/интерстициелната фиброза (п = 0,045). Кога ги анализиравме само пациентите со тешка форма на болест (нефротски синдром; пациенти третирани со имуносупресија), преживувањето на пациентите беше асоцирано само со степенот на тубулоинтерстициелните промени (п = 0,018). Анализирајќи ги изолирано пациентите со лесна клиничка форма, најдовме дека само сегментната гломерулска склероза има предиктивна вредност за реналното преживување.

Клучни зборови: ИгА нефропатија, гломерулонефрит, тубулоинтерстициелни промени, ренална инсуфициенција.

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