Pathology - Research and Practice 215 (2019) 152533

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Is it possible to predict parameters of the Oxford classification of primary IgA Nephropathy from clinical laboratory data? Focus on the role of segmental glomerulosclerosis subtypes

Maria Luiza Gonçalves dos Reis Monteiro[a,1], Matheus Rodrigues Vieira[a,1], Lívia Helena Morais Pereira[a], Liliane Silvano Araújo[a], Crislaine Aparecida Silva[a], Lúcio Borges Araújo[b], Laura Penna Rocha[a], Marlene Antônia dos Reis[a], Juliana Reis Machado[a,*]

[a] Federal University of Triângulo Mineiro, Praça Manoel Terra, 330, 38015-050, Uberaba, MG, Brazil
[b] Federal University of Uberlândia, Av. João Naves de Ávila, 120, Santa Mônica, Uberlândia, MG, 38408-100, Brazil

ARTICLE INFO

Keywords:
IgA Nephropathy
Berger's disease
Segmental sclerosis
Oxford classification

ABSTRACT

Introduction: IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world and has a broad range of histological and clinical manifestations, ranging from morphologically normal to globally sclerotic glomeruli with clinical manifestations varying from isolated hematuria to end stage renal disease. This study aims to assess sensitivity, specificity and accuracy of clinical data at the time of biopsy in predicting 2017 updated Oxford classification parameters and to investigate if subtypes of segmental sclerosis (FSGS) influence clinical presentation.

Material and methods: Renal biopsies from 103 patients with IgAN were analyzed. Oxford classification was updated and FSGS lesions were subclassified. ROC curves, univariate and multivariate logistic regression were used.

Results: In Oxford classification, the majority of patients had mesangial hypercellularity in less than a half of glomeruli (M0), did not have endocapillary hypercellularity (E0), had segmental glomerulosclerosis (S1), had interstitial fibrosis and tubular atrophy in more than a half of the sample (T2) and had no crescents (C0). Hypertension increases the chance of M1 in 2.54x ($p = 0.02$). For each unit of increased creatinine, 2.6x more chances of E1 ($p = 0.001$). S1 is predicted by proteinuria with 75% sensitivity and 90.9% specificity ($p < 0.0001$). For each unit of increase in GFR, there is a reduction of 6% in the chance of T2 in relation to T0 ($p = 0.0001$). If hypertension, there is 5x more chances of T2 than T0 ($p = 0.01$). For each unit of increase in creatinine, there are 2.8x more chances of crescents- C ($p = 0.003$). Creatinine also showed 75.8% sensitivity and 75% specificity for prediction of C ($p = 0.002$). Inversely, for each unit of GFR, the chance of C is reduced by 4% ($p = 0.007$). Other clinical data related with C are hypertension ($p = 0.03$) and proteinuria ($p = 0.02$). To determine the role of FSGS subtypes in clinical presentation, we divided patients in S0 and S1 groups. Proteinuria was the only clinical parameter with significative difference, respectively, 0.3 (0–2.1) and 1.6 (0.02–16.2) g/24 h ($p < 0.0001$). FSGS subtypes related to proteinuria were cellular ($p = 0.03$) and peri-hilar ($p = 0.02$). Subtypes classically related to podocytopathies showed no correlation with clinical data.

Conclusion: In the future, with noninvasive methods for diagnosis of IgAN, it will be essential to predict Oxford classification parameters using clinical laboratory data for establishment of prognosis and therapeutics. We showed that Oxford classification parameters correspond to some clinical laboratory data, making this approach possible. FSGS lesions not specifically related to podocytopathies may also influence clinical parameters that affect renal disease progression.

* Corresponding author.
E-mail addresses: marialuizapatologia@gmail.com (M.L.G.d.R. Monteiro), matheusmed77@gmail.com (M.R. Vieira), liviahmp@hotmail.com (L.H.M. Pereira), lili_silvano@yahoo.com.br (L.S. Araújo), crislaine.0604@gmail.com (C.A. Silva), lucio.araujo@ufu.br (L.B. Araújo), laurapenna1@hotmail.com (L.P. Rocha), mareispatologia@gmail.com (M.A.d. Reis), julianareismachado@hotmail.com (J.R. Machado).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.prp.2019.152533
Received 6 May 2019; Received in revised form 22 June 2019; Accepted 11 July 2019

1. Introduction

Jean Berger performed the first diagnosis of IgA nephropathy in 1968 [1]. This disease is characterized by the predominant deposition of IgA immunocomplexes, which may or may not be associated with co-deposits [2]. Pathogenesis is related to abnormal hypoglycosylated IgA recognized by the immune system as an antigen, with production of antibodies that will bind to these molecules and form immunocomplexes which deposit in mesangium [3].

The relevance of this disease is such that it corresponds to the most common primary glomerulonephritis in the world, with increasing rates of diagnosis [4]. Its complexity is also significant, as IgA nephropathy has a broad range of histological and clinical manifestations, ranging from morphologically normal to global sclerotic glomeruli with clinical manifestations varying from isolated hematuria to end stage renal disease [5].

In order to standardize analysis of morphological patterns, in 2009, Oxford classification for IgA nephropathy was published with the following parameters: mesangial hypercelularity (M), endocapillary hypercelularity (E), segmental glomerulosclerosis (S) and tubular atrophy/ interstitial fibrosis (T), resulting in the mnemonic MEST [6].

In 2017, an update of this classification was published, after disclosure of results from the Working Groups of crescents and of segmental sclerosis, two of the six groups resultants of a joint endeavor of International IgAN Network and the Renal Pathology Society (IIgANN/RPS) [7]. The former group added the C parameter to the classification, transforming the mnemonic into MEST-C (Fig. 1). The latter group recommended that lesions of FSGS (focal and segmental glomerulosclerosis), S1 in Oxford classification, with morphological features typically associated with podocitopathies- tip lesions or podocyte hypertrophy- should be specified in renal biopsy reports [8], as certain types of FSGS subtypes may be related to clinical manifestations and interfere with disease prognosis [9].

FSGS is a term used to describe not only a glomerular disease which primarily affects podocytes, known as podocitopathies, but secondary phenomena of scarring due to many types of injury in other glomerular diseases [10], including IgAN. Different histologic features may reflect underlying causes of sclerotic lesions and it could be hypothesized at least three pathways by which segmental glomerulosclerosis may occur in IgAN: post-inflammatory scarring, compensatory hemodynamic changes following nephron reduction and finally primary podocyte damage, probably due to immunocomplexes of IgA1 or mediators from mesangial region [11].

Segmental sclerosis subtypes proposed by the IIgANN/RPS Working Group are perihilar sclerosis, hyalinosis, segmental sclerosing lesion with no specific features (NOS), capsular adhesion without sclerosis, collapsing lesions, tip lesion, podocyte hypertrophy, resorption droplets within podocytes, and endocapillary foam cells [9]. Nevertheless, to date, Oxford classification still does not determine the systematic subclassification of S1 lesions, as there is still a lack of studies in other centers that prove the effectiveness and significance of such approach. One of the goals of this study is to contribute to this discussion with a Brazilian cohort.

Therefore, in line with the efforts of IIgANN/RPS Working Groups, we set out to evaluate the possibility of predicting Oxford classification parameters from clinical-laboratory data and to investigate whether different subtypes of segmental sclerosis can influence clinical presentation in a Brazilian cohort of patients.

2. Material and methods

2.1. Study design

Patients included in the study underwent renal biopsy and the material was analyzed in the Department of Nephropathology of the Federal University of Triangulo Mineiro (UFTM) from 2010 to 2016. All patients signed the Free and Informed Consent Form and UFTM Ethics Committee approved the research with the protocol number 46369815.0.0000.5154. Patients were from both genders, adolescents (person aged 10 to 19 years, inclusive) and adults, with diagnosis of IgAN based in a representative sample (minimum of 8 glomeruli) for light microscopy (LM- Fig. 1A) and material for immunofluorescence (IF- Fig. 1B) and electron microscopy (TEM) analysis. Pathologic diagnosis of IgAN was based on finding of IgA-dominant mesangial or mesangial-capillary immune deposits through immunofluorescence (IF) microscopy.

Exclusion criteria were absence of IF or TEM sample, non-representative biopsy samples, biopsies from transplanted kidneys, incomplete clinical data, cases of secondary IgA deposition, inconclusive diagnoses and presence of concomitant diseases.

Slides were reviewed by a single nephropathologist, blinded to clinical data, who updated Oxford classification and subclassified segmental sclerosing lesions, ensuring consistency of the results.

2.2. Kidney biopsy evaluation

Each renal biopsy was prepared for light microscopy by cutting paraffin blocks into 3 μm sections and staining 2 slides for hematoxylin and eosin (HE), 2 slides for periodic acid silver methenamine stain (PAMS), 2 slides for Sirius Red and 2 slides for Masson´s trichrome. Each slide contained three sections. Materials used for IF were frozen in liquid nitrogen, sectioned with 6 μm thickness and marked with fluorescein isothiocyanate (FITC)-conjugated antibodies specific for human IgG, IgM, IgA, C1q, C3, Kappa, Lambda and fibrinogen. Tissue for TEM was saved for future study. TEM analysis was not performed in this study.

In order to determine the role of segmental glomerulosclerosis subtypes in clinical presentation at the time of biopsy, we first divided patients into two groups according to the presence (S1) or not (S0) of segmental sclerosis.

The method chosen for subclassification of FSGS lesions was the same as that used by Segmental Sclerosis IIgANN/RPS Working Group [10], which includes but is not restricted to Columbia's classification. If more than one subtype was found in a single glomerulus, all lesions presented were recorded. Podocyte hypertrophy was considered if present anywhere in a glomerulus with segmental sclerosis.

2.3. Definitions of clinical parameters

Hypertension was characterized by systolic blood pressure (BP) greater than 140 mmHg and diastolic BP greater than 90 mmHg. Hematuria was characterized if there were more than ten thousand red blood cells per field or presence of at least 1+ of red blood cells in urinalysis. Glomerular filtration rate (GFR) was calculated by CKD-EPI formula.

2.4. Statistical analysis

A Microsoft Excel table was prepared with clinical, laboratorial and epidemiological data from biopsy reports and morphological characteristics from renal fragments. Descriptive statistics were presented as median, 25 and 75 percentiles, mean and standard deviation. Statistical analysis was performed in programs GraphPad Prism (version 7.0) and Bioestat (version 5.0). Kolmogorov-Smirnov test was used to evaluate data normality. In cases of normal distribution and similar variances, ANOVA (F) parametric test followed by Tukey post-test and Student´s *t*-test (t) were used. In cases with non-normal distribution, Kruskal-Wallis test (H) followed by Dunn post-test and Mann Whitney test (U) were used. In contingency tables analysis, Fisher's exact-test was used ($\chi 2$). ROC curves, univariate and multivariate regressions were performed to define sensitivity, specificity and accuracy of each clinical parameter in predicting histological aspects that reflect prognosis. A significance of

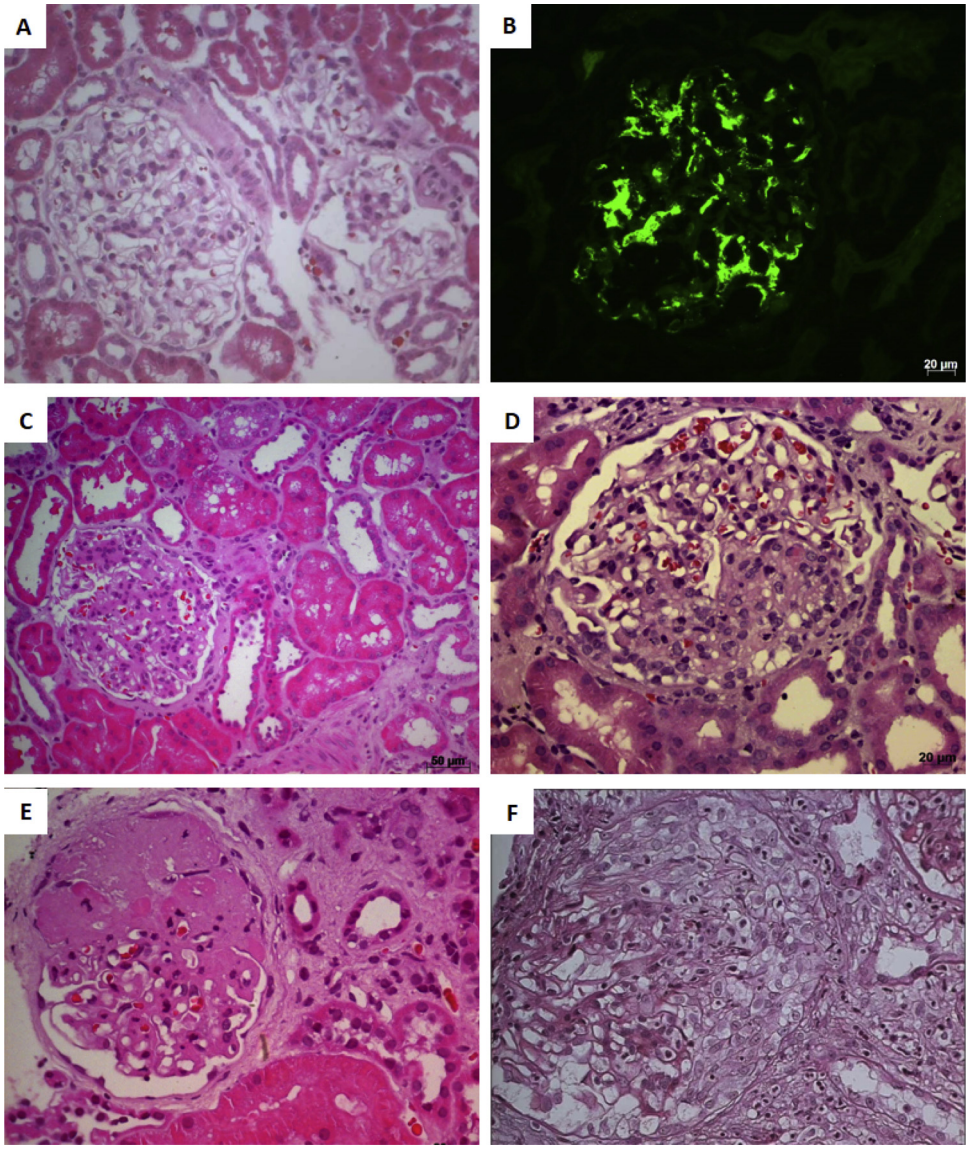

Fig. 1. Microscopic aspects of glomeruli related to IgAN diagnosis and Oxford classification. A) Normal glomerulus- light microscopy (HE) 20× 2 obj.; (B) IF IgA 40× 1 obj.; (C) Mesangial hypercellularity- M (HE) 20× 1,25 obj.; (D) Endocapillary hypercellularity-E (HE) 40× 1 obj.; (E) Segmental sclerosis (FSGS)-S (HE) 40 × 1,25 obj.; (F) Crescent- C (PS) 40× 1,25 obj.

($p < 0.05$) was adopted for all tests.

3. Results

Two hundred seventy two cases were analyzed between 2010 and 2016.

At first, exclusion criteria were absence of material for immunofluorescence analysis or light microscopy (n = 23); incomplete clinical data (n = 37) and transplanted patients (n = 9). Then cases with inconclusive diagnosis- focal, segmental or not predominant IgA deposits in IF analysis, which were suspicious but did not allowed a definite diagnosis of IgA nephropathy (n = 52) and secondary IgA nephropathy (n = 6) were excluded. The presence of concomitant diseases such as diabetes, overlapping glomerulopathies, neoplasia, among others (n = 9); and non-representative sample, with less than eight glomeruli (n = 33) were also exclusion criteria. After exclusions, a group of 103 patients was obtained (Flowchart 1 below).

3.1. Clinical-epidemiological aspects

Most patients were Caucasians (65.02%), male (64.08%) and the mean age at the time of biopsy was 38.81 ± 12.20 years (25th-75th percentiles were 31 and 48.75 years, with six patients between 11 and 18 years old).

Most patients presented hematuria (82.52%). The median proteinuria was 1.5 g/24 h (25th-75th percentiles were 0.72 and 2.82 g/24 h), with 63.11% presenting severe proteinuria (greater than 1 g/ 24 h) and 17.47% presented nephrotic levels of proteinuria. Glomerular filtration rate (GFR) had an average of 78.28 ± 37.73 mL/min/1.73 m^2 (25th-75th percentiles were 40.43 and 95.33 mL/min/1.73 m^2). Hypertension was present in49.51%of patients.

3.2. Morphological aspects and its relation with clinical presentation

According to Oxford classification, 48.42% of the patients were M1 (Fig. 1C); 35.78% E1 (Fig. 1D); 74.75% S1 (Fig. 1E); 34.73% T1 or T2, 8.42% C1 or C2 (Fig. 1F).

In order to investigate the possibility of predicting Oxford

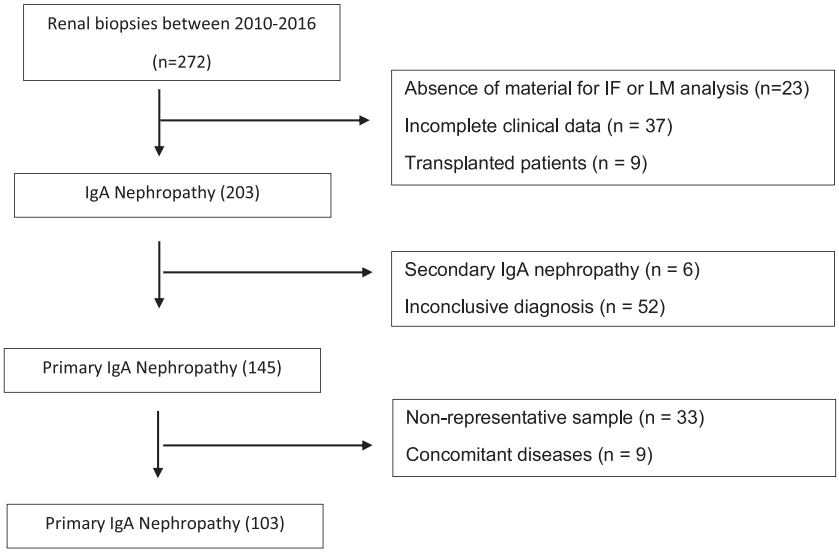

Chart 1. Exclusion factors flowchart.

classification parameters from clinical-laboratory data we performed several tests that showed each morphological parameter was related with at least one clinical laboratorial aspect.

Regarding hypercelularity parameters, M1 was associated with hypertension in univariate analysis, as hypertension increases the chance of having M1 in 2.54 times ($p = 0.024$; OR: 2.54). On the other hand, E1 was better associated with creatinine, as for each unit of increase in creatinine, there are 2.60 times more chances to have E1 ($p = 0.0018$; OR: 2.60).

As expected, S1 could be safely predicted by proteinuria, with good sensitivity (75%) and specificity (90.9%) by ROC curve with area under the curve (AUROC) of 0.86 and cutoff value of 0.61 g/day ($p < 0.0001$) (Fig. 2).

The three-tiered T parameter correlated with GFR in multivariate analysis, as for each unit of increase in GFR, there is a reduction of 6% in the chance of belonging to T2 group in relation to T0 ($p = 0.0001$, OR: 0.94). Besides, for each unit of increase in creatinine, it is 14.12 times more likely to belong to T2 than T0. T parameter is also associated with hypertension, as there is 5.08 times more chances to belong to T2 than to T0 ($p = 0.019$; OR: 5.08) if the patient is hypertensive.

Crescents were also related to several parameters, but those that stand out most are associated to renal function: for each unit of increase in creatinine, there are 2.89 times more chances to have crescents ($p = 0.0031$; OR: 2.89). Creatinine also showed good sensitivity (75.8%) and specificity (75%) for prediction of parameter C by ROC curve with AUROC of 0.7752 and cutoff value of 1.7 mg/dl ($p = 0.002$) (Fig. 3). On the other hand, GFR had an inverse relation, as for each unit of GFR, the chance of crescents is reduced by 4% ($p = 0.0079$; OR: 0.94). Other clinical data related with crescents include hypertension as if it is present, there is 9.62 times greater chance of having crescents ($p = 0.033$; OR: 9.62); and proteinuria as for each unit of increase in proteinuria, there are 1.24 more chances of having crescents ($p = 0.027$; OR: 1.24).

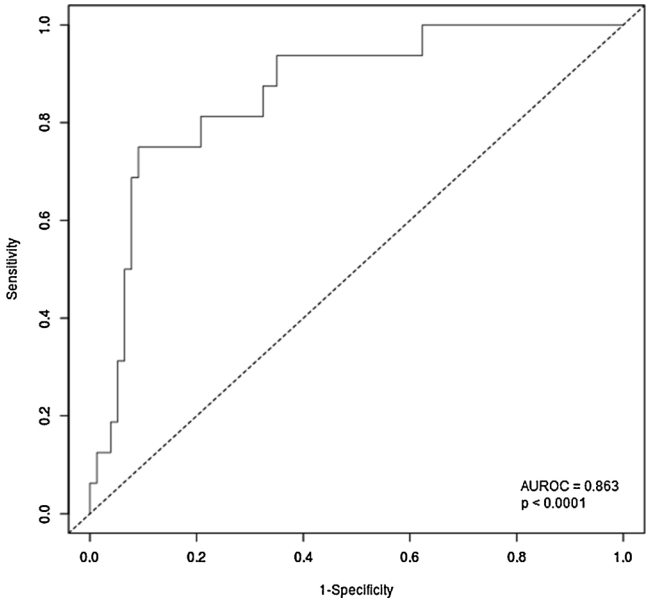

Fig. 2. Receiver operating characteristic (ROC) curve of the sensitivity plotted against 1- specificity of proteinuria for diagnosis of presence of segmental sclerosis - S1.

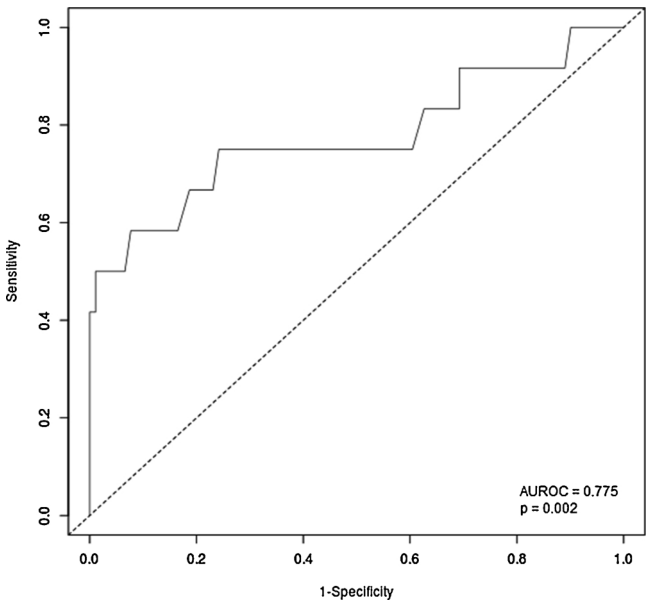

Fig. 3. Receiver operating characteristic (ROC) curve of the sensitivity plotted against 1- specificity of creatinine for diagnosis of presence of crescents.

Table 1
Clinical-epidemiological and morphological characteristics of the cases studied in the time of biopsy divided by S parameter.

	S1 (n = 77)	S0 (n = 26)	p value
Age (years)	37 (15-66)	47 (18-72)	0.1230
Females	27 (35.06%)	8 (50%)	0.2728
Race (black, brown, white)	6; 21; 50	0; 5;11	0.5089
Proteinuria	1.62 (0.02-16.2)	0.388 (0-2.1)	< **0.0001**
Arterial hypertension (present)	44 (57.14%)	7 (43.75%)	0.4111
Hematuria (present)	61 (79.22%)	15 (93.75%)	0.2880
GFR (ml/min/1.73 m^2)	63.1 (17.3-136.4)	65.05 (8.6-154.2)	0.8307
M1	42 (54.54%)	4 (25%)	**0.0523**
E1	32 (41.55%)	2 (125 %)	**0.0435**
T1 or T2	31 (40.25%)	2 (12.5%)	**0.0445**
C1 or C2	7 (9.09%)	1 (6.25%)	> 0.9999

3.3. The role of FSGS subtypes in clinical presentation

Both S0 and S1 groups were matched for clinical-epidemiological data, as there was no statistically significant difference between groups regarding age, sex, ethnicity (there was a predominance of non-blacks in both groups, representing 100% of group S0 and 92.20% of group S1, p = 0.5089), systemic arterial hypertension, hematuria and glomerular filtration rate (Table 1).

Proteinuria was the only clinical parameter with significative difference between groups, as the median proteinuria in S1 group was 1.62 (25th–75th percentiles were 0.89 and 2.86) g/24 h and in S0 the median was 0.388 (25th–75th percentiles were 0.15 and 0.66) g/24 h (p < 0.0001) (Table 1).

In contrast, most morphological characteristics were distinctive among groups (Table 1): the median percentage of glomeruli with global sclerosis (p = 0.0034), the percentage of patients classified as M1 (p = 0.0523), as E1 (p = 0.0435) and as T1 or T2 (p = 0.0445). In contrast, there was no significant difference in the percentage of patients classified as C1 or C2 (p > 0.9999).

We further divided S1 patients in morphological subtypes (Table 2) and FSGS not otherwise specified was the most prevalent, with 59.74% of cases. Next comes adhesion without sclerosis (Fig. 4A), that was found in 37.66% of cases; tip lesion (Fig. 4B) in 16.88% of cases; perihilar sclerosis in 10.38% of cases; hyalinosis in 22.07% of cases; podocyte hypertrophy in 27.27% of cases; FSGS cellular variant (Fig. 4C) in 9.09% of cases and podocyte reabsorption droplets (Fig. 4D) in 7.8% of cases. Endocapillary foam cells in sclerosis were found in 1.3% of cases and there were no collapsing lesions.

Finally, we correlated each recognized subtype with clinical data of hypertension, hematuria, GFR and proteinuria, however, statistically significant difference was found only between proteinuria and two FSGS subtypes: cellular (p = 0.0398) and peri-hilar (p = 0.0258). Surprisingly, subtypes classically related to podocytopathies showed no correlation with any clinical data alone in our cohort, nor with proteinuria: tip lesion (p = 0.6202) and podocyte hypertrophy (p = 0.5317).

Table 2
Frequency of FSGS subtypes.

FSGS subtypes	n (%)
Not otherwise specified	46 (59.74%)
Adhesion without sclerosis	29 (37.66%)
Podocyte hypertrophy	21 (27.27%)
Hialinosis	17 (22.07%)
Tip lesion	13 (16.88%)
Perihilar sclerosis	8 (10.38%)
Cellular variant	7 (9.09%)
Podocyte reabsorption droplets	6 (7.8%)
Foam cells	1(1.3%)
Collapsing	0

4. Discussion

We used clinical data at the time of renal biopsy to predict parameters of the Oxford Classification. New models for predicting disease progression involving some of the parameters of the Oxford classification and clinical data (GFR and proteinuria) have been proposed [12]. One of IIgANN/RPS Working Groups is the probabilistic modeling, which is working to optimize prediction of disease progression from morphological and clinical data at the time of biopsy [13]. This is particularly important as end stage kidney disease occurs in about a third of patients after 20 years of disease [14].

Beyond that, there have been extensive searches for non-invasive diagnostic methods of IgA nephropathy, such as the identification of miRNA in urine of rats, although in research phase [15]. In addition, another IIgANN/RPS Working Group is defining biomarkers in IgAN. Two recently described biomarkers involved in IgAN pathogenesis are FcαRI (CD68), present in myeloid cell line and involved in IgA immunocomplexes formation and transferrin receptor (CD71), present in mesangial cells, involved in immunocomplexes deposition [16].

In our study, through statistical analysis of univariate and multivariate logistic regression associated with ROC curve, we established a relationship between morphological changes in renal biopsy and different clinical manifestations.

In univariate analysis, we found a significant relationship between mesangial hypercellularity (M) and hypertension. Thus, the presence of hypertension increases the probability of the patient to belong to M1 group. On the other hand, a prognostic study of renal function found no significant difference in mean arterial pressure (MAP) values between groups M0 and M1 [17]. Hypertension is related to increased intravascular volume and inadequate control of renin-angiotensin-aldosterone system (RAAS) [18]. Therefore, increased levels of circulating angiotensin will bind to receptors in mesangial cells, leading to cell proliferation [19], which may explain the possible relationship between mesangial hypercelularity and hypertension.

Creatinine values presented a direct and strong relationship with endocapillary hypercellularity, associated with a greater chance of belonging to E1 group. This relationship is probably related to obliteration of glomerular capillaries in cases of endocapillary hypercelularity, which disturbs blood flow and reflects in loss of renal filtration function, with increased serum creatinine levels.

Although in Oxford cohort itself and other similar studies this relation between E1 and renal dysfunction was not find and E1 have only been correlated with response to immunosuppression, recent studies in adults and children have indeed shown worse prognosis in the presence of endocapillary hypercelularity in IgAN due to the association of E1 with renal function.

In a study conducted in the UK with 147 adults without immunosuppression, E1 was one of the predictors of evolution for ESRD [20]. A Brazilian study with 54 children followed for 90 ± 60 months showed that variables associated with renal survival at the time of first renal biopsy were only proteinuria and endocapillary hypercelularity [21].

In our study, proteinuria showed good specificity (90.9%) and sensitivity (75%) to predict parameter S1. Other studies also found a positive relationship between S1 parameter and levels of proteinuria [22]. Segmental glomerulosclerosis represents an irreversible secondary lesion in glomeruli. This change leads to damage of the filtration barrier, triggering proteinuria, which is one of the clinical data that best correlate to renal prognosis, and interferes in treatment decisions [17]. Thus, proteinuria is a good indicator for the presence of S1. Proteinuria was present in most cases in our study (85.43%), maybe due to biopsy indications that include the presence of persistent proteinuria in more

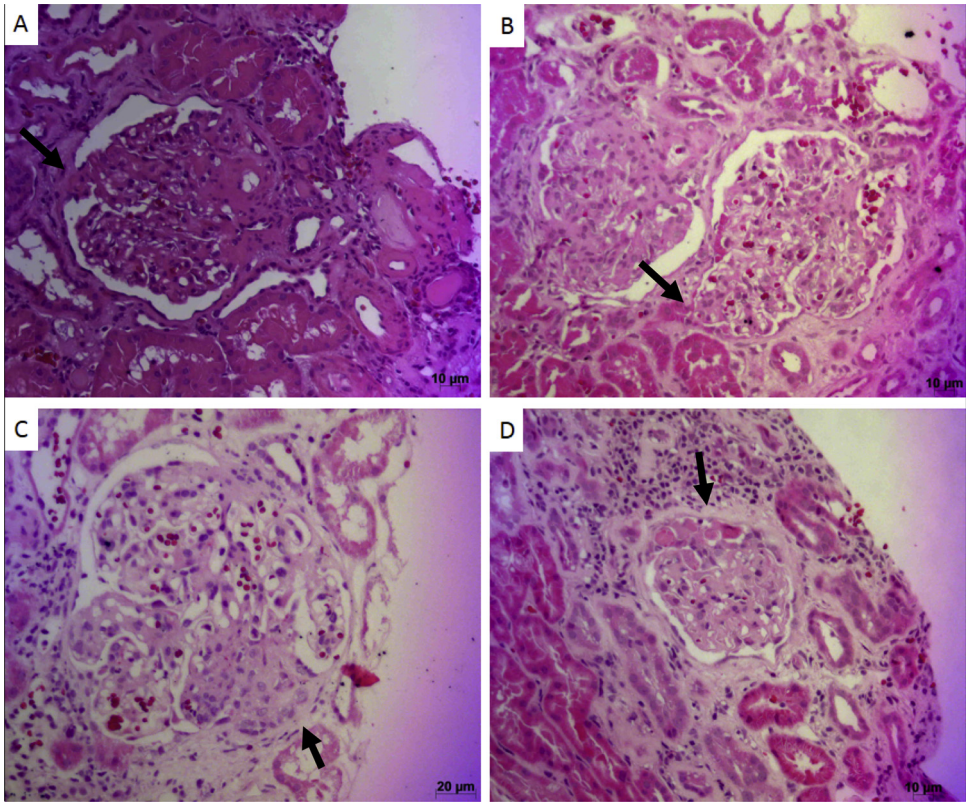

Fig. 4. Some examples of segmental sclerosis subtypes. (A) Adhesion without sclerosis- arrow (HE) 20× 1 obj.; (B) Tip lesion- arrow (HE) 20 × 1 obj.; (C) Cellular variant (HE) 40× 1 obj.; (D) Podocyte reabsorption droplets- arrow (HE) 20× 1 obj.

advanced degrees of disease.

Regarding prediction of parameter T from clinical data, it was found that the presence of hypertension increases the chances of belonging to T2 group than T0. The most commonly used prognostic evaluation considers high levels of MAP as a factor of worse prognosis. Not coincidentally, in histopathological analysis, the presence of tubular atrophy/interstitial fibrosis (T) is also used for prognostic evaluation [17].

Still regarding the parameter T, higher creatinine rates increased the patient's chances of being in T2 group compared to T0, in other words, having interstitial fibrosis and tubular atrophy, the so-called tubulointerstitial repercussions, in more than 50% of the area sampled in biopsy. Similarly, in multivariate analysis, GFR presented an inverse relation to T parameter, that is, the greater GFR the lower the chance of belonging to T2 group compared to T0. Similar findings have been reported in other publications, with a significant relationship between GFR and creatinine ratio with parameter T [22]. Thus, lower creatinine rates and increased GFR are related to reduction of tubulointerstitial repercussions, being a good indicator for parameter T.

The presence of crescents in glomeruli is correlated with worse prognosis independent of clinical data at the time of biopsy and of other MEST parameters of Oxford classification [23], being a more severe histological lesion, which affects renal function. In our study, values of creatinine, GFR, proteinuria and hypertension presented a positive and significant correlation with presence of crescents. An elegant study dealing with risk prediction in IgAN also correlated crescents with the presence of hypertension and proteinuria, which are poor prognostic parameters [17].

Therefore, the exciting discoveries of molecular mechanisms and biomarkers involved in IgAN and the description of probabilistic models to evaluate disease progression may in the future allow a non-invasive diagnosis of this glomerulopathy. In this context, it will be extremely important to have available methods to predict histological parameters related to poor clinical evolution.

Our findings endorse evidences that points to a close relationship between clinical and histopathological parameters to an extent that, in the future, could be used as a diagnostic approach.

For a better characterization of these relations, there have been several searches about the role of FSGS subtypes, especially those with morphology suggestive of Podocitopathies, in clinical presentation and evolution of the disease.

In our cases, proteinuria was the clinical data related to the presence of segmental sclerosis (S1) and it is also known to be associated with progression to chronic kidney disease [24].

Not coincidentally, by separating S1 group into subtypes, we found that, among clinical parameters, there is a positive and significant correlation only with proteinuria and in two subtypes, FSGS cellular variant and peri-hilar, characteristically not related to Podocitopathies.

Previous researches showed that subtypes of glomerulosclerosis apparently related to proteinuria are tip lesion and podocyte hypertrophy [9]. This difference may be related to different inclusion factors of the studies, as in Oxford Classification cohort [9] it was established minimum levels of proteinuria and GFR, which was not done in our study. These differences may also be due to variations in the presentation of IgAN around the world, possibly due to ethnic factors [25].

Our study points to the need to continue investigating the relationships between subtypes of segmental sclerosis and clinical presentation.

5. Conclusions

We believe that in the future, with the discovery of noninvasive methods for diagnosis of primary IgA Nephropathy, it will be essential to predict parameters of Oxford classification using clinical-laboratory data. Thus, non-invasively, it would be possible to establish prognosis and the best therapeutic strategy. We demonstrated in this study that all

parameters of the Oxford classification correspond to some clinical-laboratory data, which makes this approach possible.

Our results point to evidence that lesions of segmental sclerosis not specifically related to podocytopathies may also influence clinical parameters that affect the evolution of renal disease, such as proteinuria. Thus, we advocate the incorporation of the subclassification method of the S parameter into the routine of renal biopsy evaluation in order to contribute to further clarification of pathophysiology. The future will determine a consensus about the role of each subtype in the evolution of patients and if there is sense in maintaining this method.

The variety of segmental glomerulosclerosis subtypes that can be found in each glomerulus and in each renal biopsy is still a challenge in establishing the degree of influence of each subtype on clinical manifestations alone. Available studies are rare, requiring further evaluation in different populations to confirm and reinforce our results.

Acknowledgements

The authors appreciate the financial support of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and Fundação de Ensino e Pesquisa de Uberaba (FUNEPU).

The authors appreciate the help of the following employees from Federal University of Triangulo Mineiro, General Pathology Discipline and Nephropatology service: Alberto Borba, Edson Santos, João Noberto, José Henrique Cruvinel (*in memorian*), Lívia Alves and Vandair Gonçalves.

References

[1] J. Berger, N. Hinglais, Intercapillary deposits of IgA-IgG, J. Urol. Nephrol. 74 (1968) 694–695.
[2] Y.K. Seedat, B.C. Nathoo, K.B. Parag, I.P. Naiker, R. Ramsaroop, IgA nephropathy in blacks and Indians of Natal, Nephron 50 (1988) 137–141.
[3] G. D'Amico, Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors, Am. J. Kidney Dis. 36 (2000) 227–237.
[4] H. Suzuki, R. Fan, Z. Zhang, et al., Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity, J. Clin. Invest. 119 (2009) 1668–1677.
[5] G. D'Amico, Idiopathic IgA mesangial nephropathy, Nephron 41 (1985) 1–13.
[6] I.S. Roberts, H.T. Cook, S. Troyanov, et al., The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility, Kidney Int. 76 (2009) 546–556.
[7] I.S.D. Roberts, M.F.S. Soares, Histologic classification of IgA nephropathy: past, present and future, Semin. Nephrol. 38 (2018) 477–484.
[8] H. Trimarchi, J. Barratt, D.C. Cattran, et al., Oxford classification of IgA nephropathy 2016: an update from the IgA nephropathy classification working group, Kidney Int. 91 (2017) 1014–1021.
[9] S.S. Bellur, F. Lepeytre, O. Vorobyeva, et al., Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy, Kidney Int. 91 (2017) 235–243.
[10] Y.J. Kim, M.H. Han, Practical application of Columbia classification for focal segmental glomerulosclerosis, Comput. Biomed. Res. (2016) 1–7.
[11] K. El Karoui, G.S. Hill, A. Karras, et al., Focal segmental glomerulosclerosis plays a major role in the progression of IgA nephropathy. II. Light microscopic and clinical studies, Kidney Int. 79 (2011) 643–654.
[12] S. Tanaka, T. Ninomiya, R. Katafuchi, et al., Development and validation of a prediction rule using the Oxford classification in IgA nephropathy, Clin. J. Am. Soc. Nephrol. 8 (2013) 2082–2090.
[13] L.P. Bartosik, G. Lajoie, L. Sugar, D.C. Cattran, Predicting progression in IgA nephropathy, Am. J. Kidney Dis. 38 (2001) 728–735.
[14] C.A. Roufosse, H.T. Cook, Pathological predictors of prognosis in immunoglobulin A nephropathy: a review, Curr. Opin. Nephrol. Hypertens. 18 (2009) 212–219.
[15] Q.H. Min, X.M. Chen, Y.Q. Zou, et al., Differential expression of urinary exosomal microRNAs in IgA nephropathy, J. Clin. Lab. Anal. 32 (2018) 1–9.
[16] S.M. Lechner, C. Papista, J.M. Chemouny, et al., Role of IgA receptors in the pathogenesis of IgA nephropathy, J. Nephrol. 29 (2016) 5–11.
[17] S.J. Barbour, G. Espino-Hernandez, H.N. Reich, et al., The MEST score provides earlier risk prediction in lgA nephropathy, Kidney Int. 89 (2016) 167–175.
[18] M.C. Acelajado, D.A. Calhoun, Resistant hypertension, secondary hypertension, and hypertensive crises: diagnostic evaluation and treatment, Cardiol. Clin. 28 (2010) 639–654.
[19] K.N. Lai, L.Y. Chan, S.C. Tang, et al., Mesangial expression of angiotensin II receptor in IgA nephropathy and its regulation by polymeric IgA1, Kidney Int. 66 (2004) 1403–1416.
[20] A. Chakera, C. MacEwen, S.S. Bellur, L.O. Chompuk, D. Lunn, I.S. Roberts, Prognostic value of endocapillary hypercellularity in IgA nephropathy patients with no immunosuppression, J. Nephrol. 29 (2016) 367–375.
[21] R.C. Fabiano, S.A. Araújo, E.A. Bambirra, E.A. Oliveira, A.C. Simões e Silva, S.V. Pinheiro, The Oxford Classification predictors of chronic kidney disease in pediatric patients with IgA nephropathy, J. Pediatr. 93 (2017) 389–397.
[22] X. Zhu, H. Li, Y. Liu, et al., Tubular atrophy/interstitial fibrosis scores of Oxford classification combined with proteinuria level at biopsy provides earlier risk prediction in lgA nephropathy, Sci. Rep. 7 (2017) 1–6.
[23] M. Haas, J.C. Verhave, Z.H. Liu, et al., A multicenter study of the predictive value of crescents in IgA nephropathy, J. Am. Soc. Nephrol. 28 (2017) 691–701.
[24] G. Remuzzi, P. Cravedi, Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease, Br. J. Clin. Pharmacol. 76 (2013) 516–.
[25] M. Mubarak, Oxford classification of IgA nephropathy: broadening the scope of the Classification, J. Nephropathol. 1 (2012) 13–16.