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Research Article

Histopathological Features of Primary (Idiopathic) Focal and Segmental Glomerulosclerosis (FSGS) In Renal Biopsies: A Retrospective Study about Relevance of Glomerular Findings

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ABSTRACT

Background: Focal and Segmental Glomerulosclerosis (FSGS) is considered one of the main causes of nephrotic syndrome and end-stage renal disease (ESRD). It is a glomerulopathy characterized by podocyte injury and proteinuria. The typical presentation shows collapse and sclerosis of a segmental pattern in the glomerulus. However, nonspecific morphological changes can be found in the glomeruli with FSGS, mainly in more recent stages. This research aims to describe all the morphological findings found in idiopathic FSGS cases and to study the statistical relevance between them and the disease.

Methods: A total of 146 biopsies diagnosed with idiopathic FSGS were selected for analysis. Glomerular histological criteria were analyzed under an optic microscope including typical segmental sclerosis, global sclerosis, hyperplasia and hypertrophy of podocytes and parietal epithelial cells (PECs), presence of collapse of glomerular capillary loops, presence of adhesions, glomerular hypertrophy, among others, and were categorized as present or absent, in the biopsies studied.

Results: Bivariate associations revealed that glomerular segmental sclerosis, global sclerosis, segmental endocapillar hypercellularity, glomerular increased size and number of glomeruli with increased size, podocytes with segmental hypertrophy, PECs with segmental hypertrophy and global hyperplasia showed a tendency towards statistical significance for association with idiopathic FSGS.

Conclusions: We believe that the data we found can assist pathologists in their diagnostic routine, providing additional information in biopsies that do not present specific characteristics for histopathological FSGS diagnoses.

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KEYWORDS

Segmental Glomerulosclerosis; Glomerulosclerosis, Focal Segmental; Sclerosis; Podocytes, Histopathological features

INTRODUCTION

Focal and Segmental Glomerulosclerosis (FSGS) is a glomerulopathy related to podocyte injury, characterized by the main clinical manifestation of proteinuria [1]. It constitutes a group of podocytopathies whose causes are variable, from idiopathic to secondary. The term refers to the obliteration of the glomerular capillary lumen by a focal pattern of sclerotic formation, affecting up to 49% of the glomeruli represented in the biopsy sample, and segmental, compromising up to 49% of the glomerular unit area [2]. The distinction between primary and secondary FSGS can be made on both clinical and histologic criteria, and about 80% of cases are primary or idiopathic. FSGS is believed to be closely related to minimal change disease, and both diseases are postulated to be part of the same spectrum of diseases (podocytopathies) [3].

Podocytes are epithelial cells localized on the urinary surface of the glomerular capillary tuft. These cells are essential for maintaining the integrity and openness of the capillaries. The podocytes synthesize the glomerular basement membrane, form a molecular filter in this membrane, secrete soluble factors to regulate other glomerular cell types, and oppose the high intraglomerular hydrostatic pressure [4].

The glomerulus is constituted by capillaries, lined by fenestrated endothelium, tangled up and contained within the Bowman's capsule. The capsule is lined with parietal epithelium. Capillary beds are surrounded by mesangial cells and podocytes. The mesangial cell produces mesangial matrix. This matrix comprises proteins, such as type III-IV collagens, elastic fiber, fibronectin, and laminin. All these morphological structures, together with the glomerular basement membrane, form the filtering unit of the nephron [5].

The light microscopic evaluation uses hematoxylin and eosin (H&E), periodic acid Schiff (PAS), Masson's trichrome, and Jones methenamine silver stains to assess glomerular capillary tuft, capillary walls and their endothelium, podocytes, Bowman's capsule, parietal epithelium, mesangial cell, and mesangial matrix. The resolution achieved by optical (light) microscopy allows the discernment of morphologic features of structures related to global or focal glomerulosclerosis in routine nephropathological biopsies [6].

The glomerular histological pattern observed in FSGS is not specific to this disease, encompassing diverse clinicopathological entities characterized by primary podocyte injury [7]. The pathogenesis of the FSGS indicates that the podocyte depletion, hypertrophy of the remaining podocyte, endothelial cell injury due to compensatory intracapillary hypertension, interactions among the glomerular capillary loop and parietal epithelial cell, and mesangial changes lead to progressive sclerosis, which begins in a segmental and focal way [8].

This research aims to describe all the morphological findings that can be found in cases of idiopathic FSGS and to study the statistical relevance among them and the disease. This study complies with ethical standards and does not require the informed consent form (CAAE: 50988521.0.0000.5411).

MATERIALS AND METHODS

The study was conducted at the Hospital das Clinicas of the Faculty of Medicine of Botucatu (HCFMB/UNESP). The service covers 75 municipalities and is responsible for more than 2.0 million people. The review period for renal biopsy cases was between 2011 and 2021.

This was a descriptive and retrospective study involving detailed histopathological evaluation of biopsies from native and transplanted kidneys of cases diagnosed as idiopathic FSGS. Histological and immunofluorescence scores were used for the study cases. Cases presenting insufficient material for histological evaluation were excluded. Primary FSGS was classified histologically according to the criteria of the Columbia classification. The morphological findings of the variants were also statistically analyzed for the cases selected in this study.

All renal biopsies were selected for material suitability, defined as a minimum of 5 glomeruli. The processing technique for all biopsies included fixation parameters in Duboscq-Brazil, paraffin inclusion, and 3μm thick sections. The stains used were hematoxylin-eosin (HE), periodic acid-Schiff (PAS), methenamine silver, and Masson's trichrome using the usual methods.

The usual immunofluorescence reports available were studied. When necessary, frozen samples were subjected to a new immunofluorescence study.

All glomerular compartments were examined in biopsy samples. Data analysis referred to the presence or absence of the following criteria (morphological variables): representativeness of the sample, total number of glomeruli, global sclerosis (Figure 1A), number of glomeruli with global sclerosis, segmental sclerosis (Figure 1B), number of glomeruli with segmental sclerosis, segmental or global endocapillary hypercellularity (Figure 1C), adhesion of the capillary tuft to the cells parietal epithelial cells (PECs), hyalinosis, collapse of glomerular loops, increased matrix mesangial and mesangial cellularity, perihilar sclerosis, apical sclerosis, segmental or global foam cells, presence of glomerular hypertrophy (number of hypertrophic (size increased) glomeruli, presence of hypertrophy of segmental podocytes and global podocytes, segmental and global podocyte hyperplasia, segmental and global PECs hypertrophy (Figure 1D), segmental and global PEC hyperplasia (Figure 1D), segmental and global pseudo crescents, segmental and global crescents, segmental and global extrinsic pericapsular fibrosis in Bowman's Capsule, glomerular fibrinoid necrosis, polymorphonuclear and lymphomononuclear inflammatory cells.

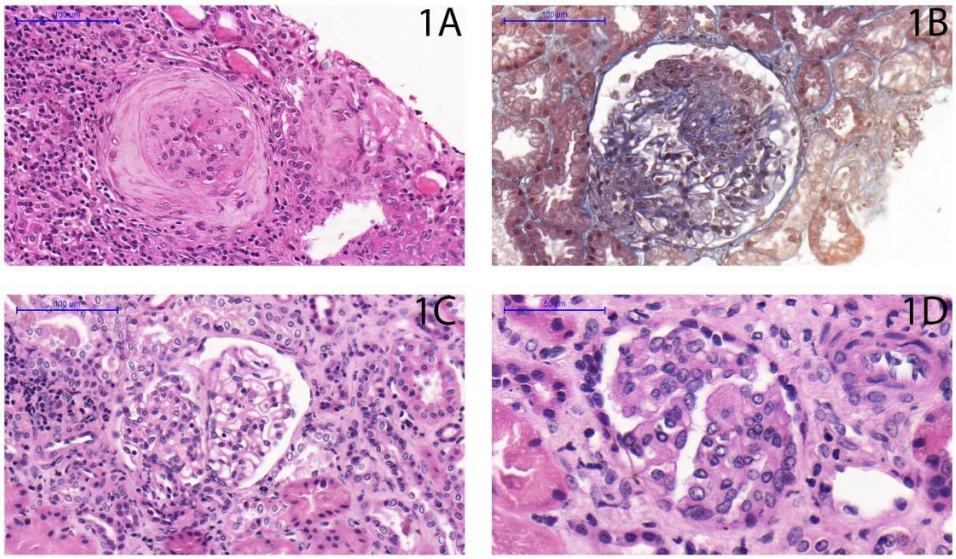

Figure 1: (1A) Presence of global glomerulosclerosis (HE staining – 200x magnification); (1B) presence of segmental glomerulosclerosis and podocyte hypertrophy Masson staining – 200x magnification); (1C) presence of segmental endocapillar hypercellularity and presence of lymphomononuclear inflammatory cells (HE staining – 200x magnification); (1D) presence of global hypertrophy and hyperplasia PECs (HE staining – 400x magnification).

The evaluation of clinical chronic kidney diseases was obtained through the analysis of medical records, collecting the following epidemiological data: age at the time of biopsy, sex, ethnicity, place of birth, origin, professional activity, whether pregnant or postpartum (for women of fertile age), previous diseases, underlying disease that led to graft loss (in cases of biopsies of renal allograft transplant), and whether the patient had Systemic Arterial Hypertension or Chronic Kidney Disease (classification of CKD, according to the Glomerular Filtration Rate, an equation developed by the Chronic Kidney Disease Epidemiology Collaboration). Secondly, some laboratory data, also at the time of the biopsy, such as the presence of proteinuria, microscopic hematuria, and serum urea and creatinine values were also collected.

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 21 (IBM Corp., Armonk, NY, USA). Qualitative data were presented as frequencies and percentages. Independent t-tests were performed to compare continuous variables between groups, and the results were presented as measures of central tendency (mean ± standard deviation and median). The Chi-square test was used to compare categorical variables. Statistical significance was defined as $p < 0.05$. Histological findings were represented as categorical variables, and bivariate associations were estimated using simple linear regressions with Poisson response for categorical outcomes, or binary/normal for numeric outcomes. The variables that presented an association with $p < 0.20$ were taken to adjust a multiple regression with Poisson or normal response. In this regression, statistical significance was defined at $p < 0.05$. This study was based on a careful analysis under optical microscopy, without using the ultrastructure tool.

RESULTS

From a sample of 146 biopsies selected for the study, utilizing the criterion of having more than 5 glomeruli on the slides, a significant representation of 90.63% was obtained. Within this group, the morphological characteristics were analyzed quantitatively, evaluating the presence or absence of each finding in the sample as described in Table 1. Some of these morphological features were subcategorized as described in Table 2.

Glomerular histopathological findings	TOTAL (%)
Segmental sclerosis	64 (55.17%)
Global sclerosis	82 (70.69%)
Adhesion	111 (95.9%)
Hyalinosis	50 (43.10%)
Collapse	72 (62.07%)
Increased mesangial matrix	82 (70.69%)
Increased mesangial cellularity	48 (41.38%)
Perihilar sclerosis	14 (12.07%)
Apical sclerosis	12 (10.34%)
Segmental endocapillary hypercellularity	17 (14.66%)
Global endocapillary hypercellularity	6 (5.17%)
Segmental foam cells	5 (4.31%)
Global foam cells	0 (0.00%)
Glomerular hypertrophy	86 (74.14%)
Podocytes general changes	103 (88.79%)
Podocytes hypertrophy	98 (84.48%)
Podocytes hyperplasia	58 (50.00%)
Podocytes with segmental hypertrophy	62 (53.45%)
Podocytes with global hypertrophy	59 (50.86%)

Table 1: The values demonstrate glomerular morphological characteristics (histopathological findings) and the percentage of presence in the microscopic analysis.

Glomerular description per biopsy	TOTAL (%)
Number	
0-5	11 (8.59%)
6-10	42 (32.81%)
11-20	53 (41.41%)
21-30	14 (10.94%)
>30	8 (6.25%)
Segmental sclerosis	
0	53 (45.69%)
1-4	59 (50.86%)
>4	4 (3.45%)
Global sclerosis	
0	34 (29.31%)
1-4	62 (53.45%)
5-10	10 (8.62%)
>10	10 (8.62%)
Increased size	
0	27 (23.28%)
1-4	69 (59.48%)

Table 2: Quantitative description of the number, presence of sclerosis, and size of glomeruli in the sample.

Similarly, clinical and laboratory data were collected from patients with the selected biopsies. Quantitative analyses assessed the presence or absence of clinical-laboratory data, as shown in Table 3. Bivariate associations were estimated using simple linear regressions with Poisson response. The variables that showed an association with $p < 0.20$ were taken to adjust a multiple regression with a Poisson response. In this regression, associations were considered statistically significant if $p < 0.05$ and trending towards significance if between 0.05 and 0.2. The interpretation of the direction of the association, the Relative Risk from Poisson Multiple Regression (RR) was analyzed. If $RR < 1$, then FSGS decreases in the presence of the morphological criteria. If $RR > 1$, the occurrence of FSGS increases in the presence of the morphological criteria.

Glomerular segmental sclerosis (showing from 1 to 4 glomeruli), global sclerosis (showing from 5 to 10 glomeruli), segmental endocapillary hypercellularity, increased glomerular size and number of glomeruli with increased size (from 1 to 4), podocytes with segmental hypertrophy, and PECs with segmental hypertrophy and global hyperplasia showed a tendency towards statistical significance for association with FSGS (Table 4). The other criteria studied were not statistically relevant.

Clinical and laboratory data	TOTAL (%)
gender*	58 (50.88%)
Transplanted	72 (63.16%)
Hypertension	79 (72.48%)
CKD	98 (86.73%)
Hematuria	36 (36.73%)
PTU:	
<0,1g	28 (26.92%)
0,1-1g	23 (22.12%)
1-3g	26 (25.00%)
UREA **	85 (79.44%)
Creatinine ***	87 (82.08%)

Table 3: Clinical and laboratory data collected from patients regarding the selected biopsies.

The clinical data "gender"* refers to the female gender; CKD refers to Chronic Kidney Disease; PTU: proteinuria; UREA** The clinical data "Urea" refers to values between 19 and 42 mg/dL; Creatinine***, The clinical data "Creatinine" refers to values between 0.6 and 1.2 mg/dL;

Morphological criteria	RR*	p
Glomerular Segmental sclerosis (from 1 to 4)	66.3	0.13
Glomerular Global sclerosis (from 5 to 10)	0.01	0.11
Segmental Endocapillary Hypercellularity	9,34	0.17
Increased glomerular size	7.81	0.19
Number of glomeruli with increased size (from 1 to 4)	26.25	0.12
Podocytes with segmental hypertrophy	72.07	0.66
Podocytes with segmental hyperplasia	0.02	0.15
Podocytes with global hypertrophy	5.03	0.319
Podocytes with global hyperplasia	0.35	0.53
PECs with segmental hypertrophy	259.56	0.08
PECs with segmental hyperplasia	0	0.11
PECs with global hypertrophy	0.43	0.57
PEC with global hyperplasia	112.94	0.1

*RR > 1 indicates that this morphological criterion is more frequent in FSGS

Table 4: Association between morphological criteria and diagnosis of FSGS: bivariate associations by multiple regression with Poisson response.

DISCUSSION

In this paper, we evaluated 146 kidney biopsies with 33 histopathological features studied from the point of view of statistical relevance in a sample of pre-selected cases diagnosed with idiopathic FSGS. Although FSGS was characterized by segmental glomerulosclerosis, other findings may be found in biopsies. A spectrum of histological features allows us to sort events into recent or late, even though it is not possible to define etiology exclusively by histology [9].

The presumed pathogenesis of this condition involves a sequence of events: damage to endothelial and epithelial cells, leading to increased glomerular permeability for proteins and their accumulation in the mesangial matrix. This accumulation promotes mesangial cell proliferation, along with macrophage infiltration and extracellular matrix accumulation, ultimately resulting in segmental glomerulosclerosis. Consequently, podocytes lose their ability to proliferate, undergoing abnormal distension (hypertrophy) in an attempt to maintain the filtration barrier. If this compensatory mechanism fails, it leads to segmental dilation of the glomerular capillary loop, followed by fibrous adhesion to Bowman's capsule and eventual segmental sclerosis. Injury may also cause vacuolization in podocytes, and foam cells and lipid droplets might be present [10,11]. There is an activation of parietal epithelial cells (PECs), which line the internal portion of Bowman's capsule, with the purpose of repopulating the podocytes. However, hypertrophy and hyperplasia of these PECs can also aggravate glomerular injury, since when they migrate from the capsular lining to the capillary tuft, they produce hyaline matrix, further damaging the glomerulus in the context of segmental sclerosis [12].

In our study, it was seen that, on average of 14 glomeruli per sample, 55.17% of the representative slides showed segmental glomerulosclerosis, with an average of 1 glomerulus affected per biopsy, with 70.69% showing global glomerulosclerosis, with an average of 3 glomeruli affected per biopsy. Glomerular hypertrophy (increased size) was also identified in 74.14% of cases, with an average of 2.6 compensatory enlarged glomeruli per biopsy. Detailed analysis of these and other histopathological alterations demonstrated that, of the representative cases, 95.69% presented adherence to Bowman's capsule, 43.10% presented hyalinosis, and collapse of the capillary loops was observed in 62.07% of cases. Mesangial alterations, such as increased mesangial matrix and cellularity, were identified in 70.69% and 41.38% of the cases. Alterations in the podocytes, both hyperplasia and hypertrophy (global or segmental), were observed in 88.79% of the samples. Hypertrophy was the most prevalent, 84.48%, followed by hyperplasia (50%), and in both cases, segmental involvement was slightly more prevalent than global involvement. The alterations in PECs followed a similar pattern: 90.52% of cases showed PEC alterations, with hypertrophy being more prevalent (85.34%) than hyperplasia (48.28%), and both were more common when affecting segments rather than the entire glomerulus. Other findings described in the literature, such as the presence of foam cells, were observed only segmentally, in 4.31% of the cases. The analysis was expanded beyond the morphological changes described in previous studies, investigating the presence of pseudo crescents, crescents, pericapsular fibrosis, fibrinoid necrosis, and inflammatory cells in representative samples.

The pseudo crescent findings were not very significant, identified in only 1 of the samples, both segmental and global, while crescents were seen in 9.48% of cases when segmental and 3.45% when global. The morphological change corresponding to pericapsular fibrosis extrinsic to Bowman's capsule was identified, when segmental, in 63.79% of cases and, in 45.69%, when global.

The presence of inflammatory cells was also a significant finding, being identified in 86.21% of cases, with the majority (83.62%) containing lymphomononuclear inflammatory cells and 25.86% containing the polymorphonuclear inflammatory cells. The incidence of hematuria and proteinuria, reduced Glomerular Filtration Rate, hypertension, and progression to chronic kidney disease are also observed in at least half of the FSGS cases. The study also included cases of patients with transplanted kidneys, which constituted 63.16% of the total cases. The incidence of Hypertension and Chronic Kidney Disease (CKD) was 72.48% and 86.73%, respectively, consistent with literature findings [13]. Laboratory data, such as hematuria, were seen in 36.73% of the cases, while proteinuria presented a value greater than 0.1 in 73.08% of the patients. Serum urea and creatinine levels were also investigated and were altered in 79.44% and 82.08% of cases, respectively. In agreement with previous studies [10], our findings showed that a Glomerular Filtration Rate (GFR) lower than 60% was present in 77.36% of cases, demonstrating the association between declined renal function and morphological alterations of FSGS.

Statistical analysis in our study showed that glomerular segmental sclerosis, global sclerosis, segmental endocapillary hypercellularity, glomerular increased size and number of glomeruli with increased size, podocytes with segmental hypertrophy, PECs with segmental hypertrophy and global hyperplasia had tendency towards statistical significance for association with idiopathic FSGS. Histologically, segmental endocapillary hypercellularity can be interpreted as endothelial injury that occurs at the beginning of the pathological process. Podocytes present intracellular changes that precede sclerosis (scarring). Segmental podocyte hypertrophy is compatible with the pathophysiology of podocyte enlargement or distension due to its inability to proliferate in this disease [11,14].

Parietal epithelial cells (PECs) exhibiting segmental hypertrophy and global hyperplasia play a significant role in the development and progression of focal segmental glomerulosclerosis. Normally lining Bowman's capsule, these PECs become activated and contribute to the formation of sclerotic lesions in FSGS by proliferating and invading the glomerular tuft, thus disrupting the epithelium and leading to scarring [15]. The other statistically relevant morphological findings encompass the established segmental lesion, glomeruli exhibiting global sclerosis as a result of late-stage disease processes, and the increase in glomerular size in unaffected glomeruli as a compensatory mechanism.

Although these morphological findings in FSGS are already described in the literature, the purpose of this study is to demonstrate that detailed morphological analysis in anatomopathological reports can offer complementary information.

LIMITATIONS OF THE STUDY

We acknowledge that this study has limitations. Our study did not use electron microscopy tools to complement the analysis under optical microscopy.

FINANCIAL SUPPORT AND SPONSORSHIP

This research was self-funded.

CONFLICT OF INTEREST

There is no Conflict of Interest.

PATIENT CONSENT DECLARATION

The Institutional Review Board waived the need for informed consent from study patients because this was a retrospective study of renal biopsy samples.

ETHICAL APPROVAL

This study complies with ethical standards and does not require the informed consent form (CAAE: 50988521.0.0000.5411).

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