Original paper

Usefulness of rebiopsy in the case of mesangial pathology

Jakub Żurawski[1], Patrycja Talarska[1], Wiesława Salwa-Żurawska[2], Katarzyna Iwanik[2], Joanna Bulak[2], Aldona Woźniak[2]

[1]Department of Immunobiology, Poznan University of Medical Sciences, Poland
[2]Chair of Pathology and Clinical Immunology, Poznan University of Medical Sciences, Poland

Immunologically different types of glomerulopathies show varied symptoms and clinical courses. Unlike in lupus nephritis, repeated biopsy is rarely performed in cases of mesangial glomerulonephritis. We reviewed 200 cases wherein rebiopsy was performed in patients with diagnosed mesangial glomerular pathology over a 30-year period and analyzed the symptoms follow-up in these cases. Further, we evaluated the morphological changes between the first and final biopsies to identify cases of histological progression and histological remission and examined the correlation between such changes and clinical symptoms. The time between the first and last biopsies ranged from 7 months to 35 years. The most common for the initial biopsy was nephrotic syndrome, followed by non-nephrotic proteinuria; other symptoms occurred rarely. Histological progression occurred at various stages of observation, ranging from within a few months to after several years. Histological progression and remission were detected in 118 and 3 patients, respectively, whereas there was no difference in morphological findings between the first and last biopsies in 79 patients. Rebiopsy is useful in patients who do not respond adequately to treatment, and especially in those with increased clinical symptoms. Moreover, electron microscopic examination is necessary to discover early signs of histological progression.

Key words: rebiopsy, mesangial glomerular pathology, nephrotic syndrome, biopsy.

Introduction

In general, it is difficult to determine the prognosis of diseases characterized by mesangial pathologies. In the last several years, the notion of "mesangial glomerulonephritis" [1, 2, 3, 4, 5] has been replaced with "IgA nephropathy" [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16], "IgM nephropathy" [17, 18, 19, 20, 21], or "IgG nephropathy" [22] based on immunological examinations. The common morphological characteristics in all 3 nephropathies are the increase in the number of mesangial cells (four and upwards) and the presence of deposits in the mesangium. Therefore, the term "mesangial glomerulonephritis" is still used in the histological or electron microscopic evaluation, and the final diagnosis is based on immunofluorescence examination. The number of mesangial cells evaluated on histological examination should be verified by the electron microscopic examination. The same applies to the quantitative evaluation of the matrix, which is a pre-requisite in the examination of preparations impregnated with silver salts in the Jones method.

All immunologically differentiated types of glomerulopathies have a variety of clinical symptoms including microhematuria, proteinuria, and nephrot-

ic syndrome, which may occur in different combinations. Moreover, the clinical course of the disease varies. While some patients may have an unfavorable early stage of the disease, other patients may not exhibit clear signs of deterioration for several years.

Unlike in lupus nephritis [23, 24, 25, 26, 27, 28, 29], rebiopsy is rarely performed in the case of mesangial glomerulonephritis and focal segmental glomerulosclerosis. Therefore, we evaluated the efficacy of rebiopsy in the case of mesangial glomerulopathy [30, 31, 32, 33, 34, 35, 36, 37, 38, 39].

This study aimed to evaluate the efficacy of repeated biopsy in the case of mesangial pathology where anticipated treatment results were not obtained, especially those with deteriorating conditions.

Material and methods

We reviewed 200 cases of rebiopsy performed in patients with diagnosed mesangial glomerular pathology over 30 years. In this period, mesangial glomerulonephritis was diagnosed in 1650 out of 5119 examined patients. Among 200 cases, 124 and 76 were adults aged 19-63 years and children aged 2-18 years, respectively. The largest groups among adult men, adult women, boys, and girls were aged 19-32, 41-50, 12-17, and 11-16 years, respectively.

Kidney tissue samples were subjected to histological, electron microscopic, and immunofluorescence examination. Paraffin-embedded tissues were stained with hematoxylin and eosin and impregnated with silver salts according to the Jones method, and PAS reaction was performed. In some cases, Masson's stain was used.

Frozen sections were subjected to direct immunofluorescence reaction with antibodies against IgG, IgA, and IgM immunoglobulin classes; C3, C4, and C1q of the complement system; and fibrinogen. In most cases, electron microscopic examination was performed.

It was not necessary to obtain ethical consent or patient consent for this study.

Statistical analysis

Due to the lack of normality of age structure and of the time between the first and last biopsy, non-parametric tests were used for the analysis. To verify the significance of differences in the length of time between the first and last biopsy, the Mann-Whitney test was used to compare two groups. To examine the correlation between the age and the time between the first and last biopsy, Spearman's rank correlation coefficient test was used. A p-value <0.05 was considered statistically significant. Statistical calculations were performed using the STATISTICA 13.3 (StatSoft) statistical package.

Results

The diagnosis of mesangial glomerulopathy based on histological examination (Figs. 1 and 2) was confirmed with the immunological examination and, in most cases, with the electron microscopic examination (Figs. 3, 4, and 5).

Immunofluorescence examination revealed the presence of IgM (78%), IgA (57%), IgG (21%), C1q (71%), C3 (43%), and C4 (28%). On the other hand, IgA and C3 predominated in patients who did not undergo repeat biopsy (1305 cases).

Out of 200 patients who underwent rebiopsy, histological progression was observed in 118 patients with a significant increase in the mesangial matrix and various degrees of interstitial lesions such as inflammatory infiltrates and fibrosis. Out of 118 patients with histological progression, 74 and 44 were adults and children, respectively. There was no difference in intensity of changes between the first and last biopsy in 79 patients, of whom 43 and 36 were adults

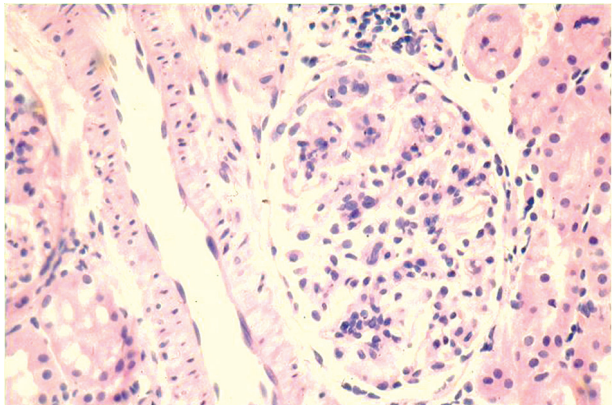

Fig. 1. Glomerulus with a significantly increased number of cells in most mesangial areas. HE staining, magnification 400×

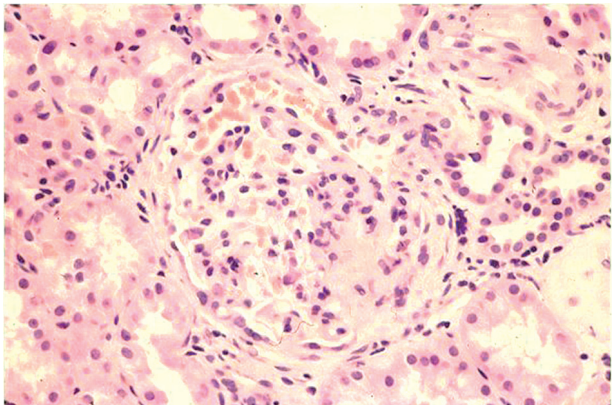

Fig. 2. Renal glomerulus with an increased number of cells in some mesangial areas with a segmental sclerosis. HE staining, magnification 400×

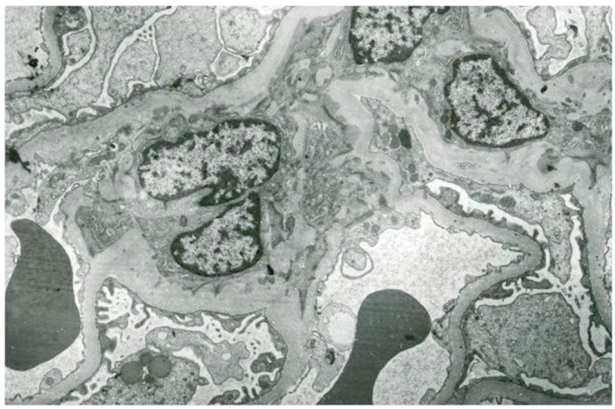

Fig. 3. A piece of glomerulus with an increased number of mesangial cells (4) and numerous deposits. Electron microscopy, magnification 4000×

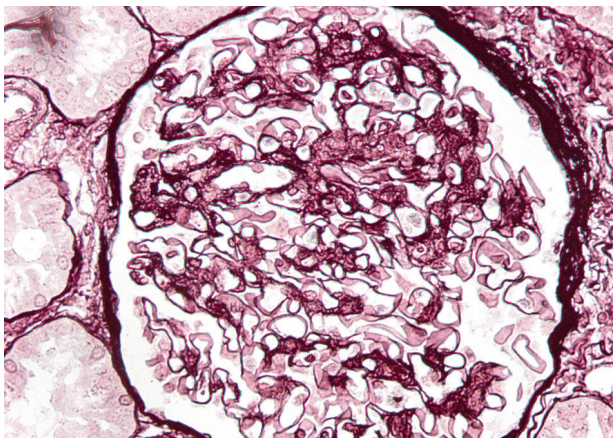

Fig. 4. Glomerulus with significant increased amount of mesangial matrix (indication of severe progression). Jones staining, magnification 1000×

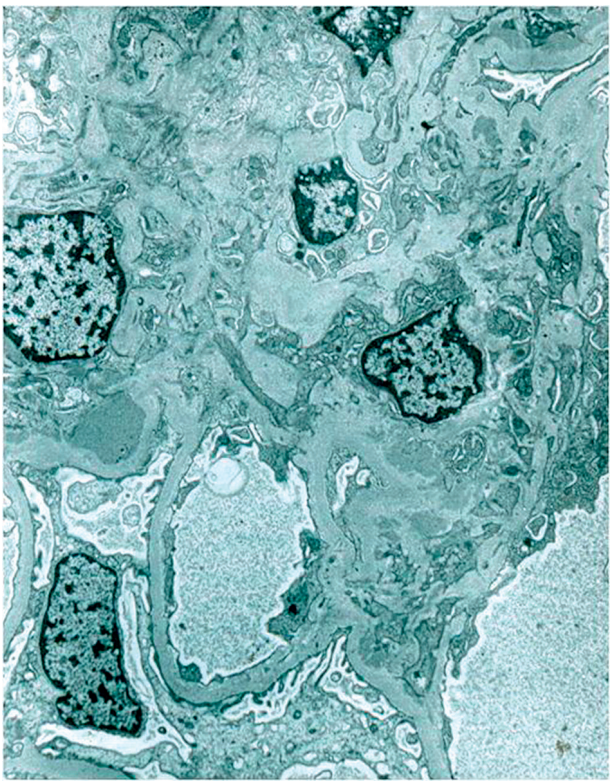

Fig. 5. Glomerulus with profuse deposits and a significantly increased amount of mesangial matrix (indication of progression). Electron microscopy, magnification 4000×

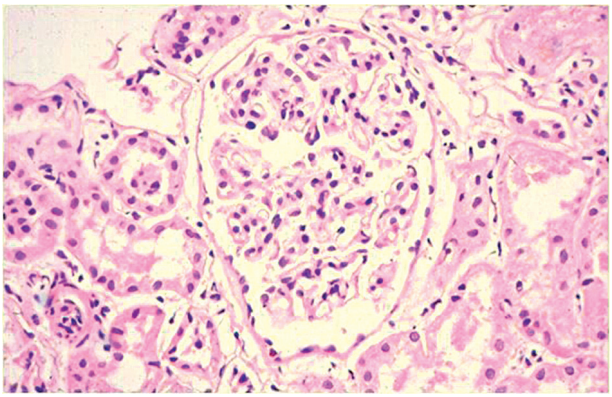

Fig. 6. Unchanged glomerulus (indication of regression). HE staining, magnification 400×

and children, respectively. Three adult patients were diagnosed with remission.

The intensity of changes indicating histological progression varied. These cases had distinct sclerosis, often with segmental sclerosis of some glomeruli. Moreover, interstitial changes (fibrosis and lymphocytic infiltration) of various intensity were detected in 3 patients. These changes were detected in 4 patients within 7-12 months.

These low-intensity changes were seen in 25 patients. In 4 cases, changes were detected only in the electron microscopic examination and consisted of a slight increase in the matrix in some mesangial area. These low-intensity changes were detected 4 to 25 years after the first biopsy.

A decrease in the number (to the normal range) of mesangial cells was considered as a sign of histological regression (Figs. 6 and 7). Additionally, we noted that the deposits visibly decreased or were not observed in an electron microscopic examination for these patients.

The time between the first biopsy and the biopsy showing histological progression varied from a few months to 35 years (in 1 patient). In adults and children, histologic progression was most often (in 41 persons) observed after 2-8 years and 3-10 years, respectively.

The follow-up of patients without histological progression varied from a few months to 30 years, and for patients with histologic remission, it was 11, 20, and 21 years. A lack of histological progression in adults was most often found (in 30 patients) within a few months up to 7 years and in children (17 patients) after 1 to 6 years. The longest follow-up in two 15-year-old children was 11 years. For adults, it was between 12 and 35 years.

The recommendation for repeat biopsy in patients who showed progression was most frequently because of a lack of improvement or an increase in clinical symptoms (increased proteinuria, poorer control of hypertension). For these patients with progression after rebiopsy, the most frequently observed clinical symptom was the nephrotic syndrome (in 57 patients: 23 adults and 34 children), followed by non-nephrotic proteinuria (in 35 patients: 30 adults and 5 children), non-nephrotic proteinuria and microhematuria (in 13 patients: 11 adults and 2 children), non-nephrotic proteinuria and hypertension (in 8 adult patients), isolated microhematuria (in 3 patients, including 2 adults), and the nephrotic syndrome and microhematuria (in 2 children).

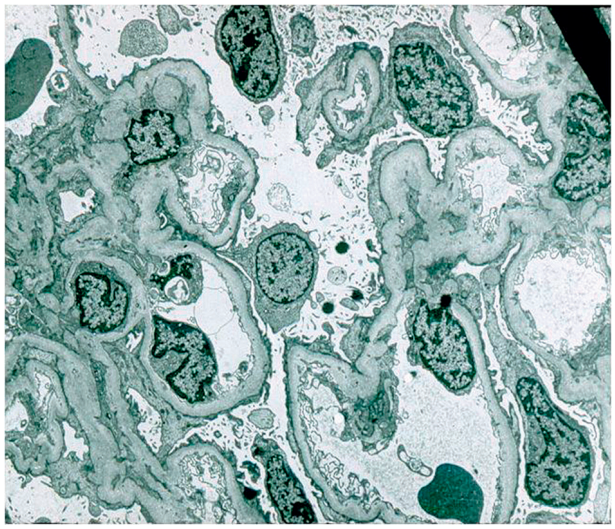

Fig. 7. Unchanged glomerulus (indication of regression). Electron microscopy, magnification 4000×

In patients without progression, the most frequent symptom for a biopsy was the nephrotic syndrome (in 33 patients: 14 adults and 19 children). In rare cases, the following symptoms were detected: non-nephrotic proteinuria (in 17 patients: 15 adults and 2 children), non-nephrotic proteinuria and microhematuria (in 9 patients: 7 adults and 2 children), non-nephrotic proteinuria and hypertension (in 9 patients: 8 adults and 1 child), isolated microhematuria (in 7 patients: 6 children and 1 adult), microhematuria and hypertension (in 3 patients, including 2 adults), and the nephrotic syndrome and microhematuria (in 1 child).

In the 3 patients identified with regression, the following symptoms were diagnosed: the nephrotic syndrome, non-nephrotic proteinuria, and micro-hematuria and non-nephrotic proteinuria in one patient each. The independent variables (predictors) were age and gender. The dependent variable was the time between the first and the last biopsy.

Age was found to be significant ($p = 0.0287$) for the time between the first and last biopsy in the group without progression and with nephrotic syndrome (Table I). For the time between the first and the last biopsy in the group with progression, age ($p = 0.0188$) was found to be significant (Table II). For the time between the first and last biopsy in the group with progression for proteinuria, gender ($p = 0.0192$) and age ($p = 0.0090$) were found to be significant. For men, the time between the first and the last biopsy is on average longer by 5.39 ±2.19 years than for women, with the other variable being constant.

Increasing the age of the examined patients by one year prolonged the period between the first and the last biopsy on average by 0.23 ±0.08 years, with the other variables being constant. Age has a greater influence than gender in the period between the first and last biopsy (Table III). Similar-

Table I. Results of forward multiple regression for the time between the first and last biopsy in the group without progression for the nephrotic syndrome

Without progression, NEPHROTIC SYNDROME Summary of regression of dependent variable: Time between the first and last biopsy [years] $R = 0.430$; $R^2 = 0.184$; Corr. $R^2 = 0.130$; $F(2.30) = 3.39$; $p < 0.0469$; Standard error of the estimate: 6.95						
n = 33	b*	Std. error with b*	b	Std. error with b	t(30)	p
Absolute term			7.761	4.343	1.79	0.0840
Gender	–0.154	0.166	–3.469	3.735	–0.93	0.3604
Age	0.382	0.166	0.240	0.104	2.30	0.0287*

** statistically significant, p < 0.05*

Table II. Results of forward multiple regression for time between the first and last biopsy in the group with progression

Progression Summary of regression of dependent variable: Time between the first and last biopsy [years] $R = 0.256$; $R^2 = 0.065$; Corr. $R^2 = 0.049$ $F(2.115) = 4.03$; $p < 0.0204$; Standard error of the estimate: 5.44						
N = 118	B*	Std. error with B*	B	Std. error with B	t(115)	p
Absolute term			3.709	1.160	3.20	0.0018
Gender	0.140	0.090	1.552	1.002	1.55	0.1241
Age	0.215	0.090	0.076	0.032	2.38	0.0188*

** statistically significant, p < 0.05*

Table III. Results of forward multiple regression for the time between the first and last biopsy in the group with progression for the symptom of proteinuria

Progression, PROTEINURIA Summary of regression of dependent variable: Time between the first and last biopsy [years] $R = 0.530$; $R^2 = 0.281$; Corr. $R^2 = 0.236$ $F(2.32) = 6.25$; $p < 0.0051$; Standard error of the estimate: 6.37						
N = 35	B*	Std. error with B*	B	Std. error with B	t(32)	p
Absolute term			–4.227	3.497	–1.21	0.2356
Gender	0.372	0.151	5.395	2.187	2.47	0.0192*
Age	0.419	0.151	0.233	0.084	2.78	0.0090*

** statistically significant, p < 0.05*

ly, in the group of patients with progression, for the symptom of proteinuria only, there was a significant positive correlation of moderate power between the age of persons and the time between the first and the last biopsy.

Discussion

The clinical image was variable in the group of patients who underwent a repeat biopsy. However, a majority of the patients including those with progression and those who were not diagnosed with intensified morphological changes had nephrotic syndrome.

Most patients with IgM nephropathy had unfavorable clinical results, suggesting that repeat biopsy is necessary. It should be stressed that in 4 cases of progression, a distinct intensification of changes was observed within 7-12 months following the first biopsy, and in the 9 other cases, the changes were seen 10-25 years later, with stable or gradually increasing intensity of clinical symptoms.

In the group of patients without progression, increased intensification of clinical symptoms was not observed with an increase in the time since the first biopsy. The lack of satisfactory treatment results suggests that repeat biopsies are important to rule out progression.

In addition, our results highlight the necessity to perform an electron microscopic examination. In this study, 8 cases had an early stage of sclerosis, which is imperceptible in histological examination. Electron microscopic examination becomes indispensable, especially when it facilitates modification of treatment which may halt the histological progress of sclerosis.

Since the number of patients with low intensity of morphological changes is small, we cannot make any binding conclusions, but it suggests a possibility of effective control of changes. There have been few reports on this in the literature.

In conclusion, repeat biopsy is recommended in every case where the clinician does not see effective treatment results. Moreover, clinicians should not rely on the intensity of clinical symptoms since, in this study, we observed progression regardless of the clinical symptoms. Reports on rebiopsies in cases of mesangial glomerulonephritis in recent years have been few, and sometimes the study cohort was small.

In the cases presented by us, the morphological image (light and electron microscopic images) was the same (cell proliferation and deposits in the mesangial areas, in the case of histological progression, an addition to the mesangial matrix) – a typical picture of mesangial glomerulopathy. In recent years, the terms "mesangial inflammation" and "glomerulopathy" have been used less frequently. They were replaced with a description of the nature of the deposits – IgA, IgM, IgG nephropathy. In most of these studies, the description of morphological changes corresponds to mesangial inflammation (glomeru-

lopathy), but often apart from them, there are also descriptions corresponding, for example, to membranous nephropathy [16].

The clinical nature and prognosis of these glomerulopathies are generally different from those of mesangial glomerulopathy. Therefore, it is necessary each time – apart from the immunomorphological result included in the name of nephropathy – to define the morphological character – absolutely including the result of electron microscopy [40].

Conclusions

The following conclusions of the study were drawn:

- There are serious difficulties in defining the prognosis of diseases characterized by changes in the glomeruli of the kidney, histologically described as mesangial glomerulopathy or mesangial glomerulonephritis.
- Our study showed that in these cases, there is no strict correlation between the stage of disease progression, the clinical symptoms, and the time between the first and last biopsy. Hence, repeat biopsy is useful in cases where no deterioration of the clinical condition is observed, but only a lack of reaction to treatment and continuous clinical symptoms.
- To confirm disease progression, especially in the early stages, it is necessary to perform electron microscopic examination.
- Moreover, the results of immunofluorescence tests showed that the majority of patients requiring rebiopsy had a high percentage of IgM, unlike 145 patients without indications for rebiopsy who had a high percentage of IgA and C3.

The authors declare no conflicts of interest.

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Address for correspondence

Jakub Żurawski
Department of Immunobiology
Poznan University of Medical Sciences Poland
Rokietnicka 8
60-806 Poznan, Poland
e-mail: zurawski@ump.edu.pl