Focal segmental glomerulosclerosis: a diagnostic problem

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Focal segmental glomerulosclerosis (FSGS) is an important clinical problem as it leads to end-stage renal disease. Clinicians have long been able to treat patients with FSGS. Therefore, the demands the clinicians make on pathomorphologists, which include the diagnosis of FSGS at a possibly early stage, are justifiable. However, early diagnosis of FSGS is difficult. The analysis involved 150 cases of FSGS diagnosed between 2003 and 2008. These constitute 14.53% of renal biopsy material of that period. The test material comes from 138 adults and 12 children. The adult group mostly included patients with albuminuria (58 patients) and nephrotic syndrome (36 patients). Smaller groups included patients with albuminuria and hypertension, erythrocyturia and albuminuria, isolated erythrocyturia. The children group mostly included patients with the nephrotic syndrome. Individual patients suffered from isolated albuminuria and erythrocyturia. In both groups, FSGS NOS lesions prevailed. However, FSGS hilar and FSGS tip lesions, as well as completely sclerotized glomeruli were also present. Diverse symptoms of diseases may pose specific difficulties in clinical diagnosis. Similarly, determination of FSGS lesion type may be difficult due to simultaneous presence of different subtypes in the same punctate.
The presence of completely sclerotized glomeruli may not be associated with the duration of the disease.

Key words: types of glomerulosclerosis, clinical manifestation, early diagnosis.

Introduction

The diagnosis of glomerulosclerosis is usually tantamount to the diagnosis of focal segmental glomerulosclerosis (FSGS). The FSGS poses an important clinical problem as it leads to end-stage renal disease in 25-30% of patients after 5 years, and in 30-40% after ten years of the disease duration [1]. The FSGS is the most common disease requiring chronic dialysis and kidney transplantation [2]. It was also found to be recurrent in 28-30% of patients following the transplantation [2, 3] as well as to develop *de novo* following the transplantation performed for other reasons [2]. On the other hand, clinicians have long been able to treat patients with FSGS [4-9]. Therefore, the demands the clinicians make on pathomorphologists, which include the diagnosis of FSGS at a possibly early stage, when chances of successful management are better, are justifiable. However, early diagnosis of FSGS is difficult. Therefore, although the morphological exponents of FSGS have been long known, new assessment criteria and morphological prognostic features are still being sought for.

In 1970, the International Study of Kidney Diseases In Children Group stated that *glomerulosclerosis focalis et segmentalis* is a separate clinical and morphological entity that differs from the minimal lesions (submicroscopic glomerulonephritis) by steroid resistance and progression leading to renal insufficiency. Earlier, it was a domi-

nant opinion that focal segmental glomerulosclerosis was a continuation of minimal lesions [10, 11]. During the next 4 decades, FSGS was studied in numerous research sites. As a result of this research, FSGS was defined as a clinical and morphological syndrome:

1) characterized by focal, segmental sclerotization of glomeruli and effacement of visceral cell foot processes;
2) leading to diffused and global sclerotic lesions.

Various terms were used to describe these lesions, starting from the simple term "sclerosis focalis" and ending at the term "sclerosis focalis et hyalinosis", used by French researchers. The latter is not quite correct [12], since hyalinization is not always (or, rather, is very rarely) present and is only a slight "undertone" of sclerotic lesions.

The diagnosis of FSGS can be problematic since the morphological lesions are not specific. They may appear in various conditions and overlap numerous glomerular processes. The initial location of lesions in the juxtamedullary region is not always revealed since that segment is not always included in the punctates. Newman *et al.* have found that lesions in juxtamedullary glomeruli are predominant at the early stage only in 2-17% of cases [13].

One can distinguish between primary (idiopathic) and secondary forms of FSGS. The secondary form includes cases of familial FSGS, associated with a genetic mutation of podocyte proteins, cases associated with viral infections, action of drugs, or being a consequence of adaptation processes. Both forms should be in turn distinguished from lesions occurring in the course of various inflammatory and proliferative processes, congenital diseases (Alport syndrome) and others [14]. Here, immunofluorescence and electron microscopy assessments are helpful in establishing the diagnosis.

Each of these groups is characterized by a number of similar changes. They are of focal and segmental character (at least at the early stage). Most commonly, the most severe lesions are observed in the segments located in the vicinity of the vascular pole. The nature of these lesions is the rise in the quantity of mesangial matrix, hypertrophy and, in some cases, proliferation of podocytes located above these lesions and capillary collapse. It is suggested that the earliest change is the presence of foam cells within the capillaries. Most probably, the foam cells are derived from endothelial cells. At later stages, the foam cells decompose and their cytoplasmic debris (including lipids) is incorporated into the sclerotic lesions. A characteristic feature is the effacement of foot processes of podocytes, particularly severe above sclerotization foci. This lesion is considered to be of great importance. Fogo thinks that if sclerotic glomeruli are found in the punctate and their presence is not accompanied by effacement of foot processes, FSGS may not be diagnosed [15].

Segmental or global mesangial hypercellularity may occur in glomeruli with sclerotic foci, but also in the remaining glomeruli as well. It is not, however, considered to be of great importance [15].

As the disease progresses, completely sclerotized glomeruli become apparent. Adhesions of capillary loops to the Bowman's capsule are relatively early formed and undergo hyalinization over time. The number of these adhesions indicates the advancement of the process. Tubular atrophy and interstitial fibrosis are generally associated with the severity of glomerular lesions. Foam cells are also sometimes found in the interstitium.

Immunofluorescence assays usually show IgM and C3 deposits, and occasionally deposits of other immunoglobulins.

Within the last 20 years, a number of observations were made regarding specific lesions present in FSGS. Based on these observations, 5 variants of the disease were distinguished [14, 15]. They include:

1) FSGS (NOS) – non-specific (classic) variant;
2) perihilar variant;
3) tip variant;
4) collapsing variant;
5) cellular variant.

The FSGS (NOS) variant is the most common variant, characterized by all features described above. The perihilar variant is characterized by sclerotization located in the vicinity of the vascular pole. The tip variant relates to cases in which the affected region is adjacent to the proximal tubule. A characteristic feature of this variant is intracapillary hypercellularity and podocyte hyperplasia and/or hypertrophy. Foam cells are often observed. Hyalinization and mesangial hypercellularity occur in varied frequency. This variant is considered to have good prognosis. The course of the disease is unfavorable only in rare cases.

The collapsing variant involves segmental or global collapse of capillary lumina, accompanied by proliferation and hyperplasia of podocytes that cover these capillaries. The segmental lesions are localized in the perihilar region and peripherally. More often, however, the lesions are global. This variant is considered to be associated with dysregulation of the podocyte phenotype. Viral infection (parvovirus) or pamidronate treatment may also contribute to this condition. Recurrences following kidney transplants are also observed. This variant can also develop *de novo* in transplants after cyclosporine treatment. It accompanies severe vascular lesions. The prognosis is therefore definitely poor.

The cellular variant is least characterized. Intracapillary proliferation leading to closure of at least 25% of the capillary loop is considered to be characteristic of this variant. Macrophages, neutrophils and lymphocytes are present besides the foam cells in the vascular lumen. Proliferation and hyperplasia of podocytes covering these lesions may also be observed. This variant may be transformed into a less cellular and more sclerotic form, non-distinguishable from classic FSGS. This variant is observed at early stages in the case of

transplantation and FSGS recurrence. Therefore, it is considered to be an early and active form of FSGS.

The authors of this classification attach a lot of importance to glomerulomegaly. They consider it to be an early exponent that signals sclerotization. Fogo *et al.*[15] claim that the presence of unnaturally large glomeruli indicates the onset of sclerotization even when no sclerotic lesions are found in the punctate. On the other hand, however, glomerular hypertrophy (with the increase in the quantity of the mesangial matrix) was observed e.g. in preeclampsia, with clinical symptoms of renal damage resolving within several weeks after delivery [16].

In recent years, much attention has been paid to podocyte changes. Increase in podocyte counts, hypertrophy, detachment from basement membranes, cytoplasmic vacuole changes were reported [6, 15, 17-20]. The authors are inclined to regard these changes as FSGS determinants.

Results of molecular podocyte assays are also pointed out. In rare cases of familial sclerotization, muta-

tions of the following genes were observed: the α-actinin 4 (ACTN4) gene, the nephrin (NPHS1) and podocin (NPHS2) gene, the CD2 (CD2AP), the Wilms tumour (WT1) gene and type IV collagen COL4A3/COL4A4 genes [15, 21-24].

Material and methods

The material included 150 kidney punctates with sclerotized glomeruli. The material originated from a set of 1031 kidney biopsies performed in the Department of Clinical Pathomorphology Medical University in 2003-2008. Cases with diagnosed glomerulosclerosis accounted for 14.53% of this set.

The patients were treated at the Faculty and Clinic of Nephrology, Transplantology and Internal Diseases, the Clinic of Pediatric Cardiology and Nephrology of the 1st Faculty of Pediatrics of the PUMS, the Poviat Hospital in Leszno and the Voivodship Hospital in Zielona Góra.
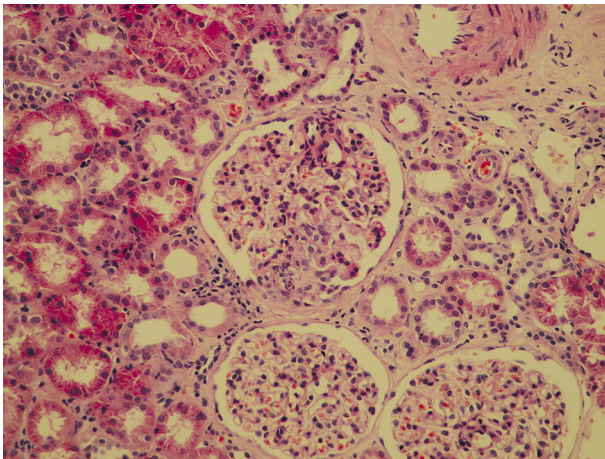

Fig. 1. Early stage of FSGS (hilar type). Increased number of cells and gain of matrix in the area of vascular pole. HE, magnification 180×
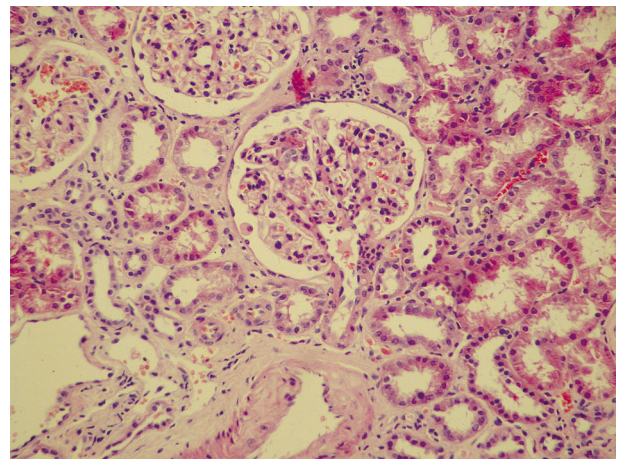

Fig. 2. Early stage of FSGS (tip type). Gain of matrix in the glomerulus in the paraurethral area of the glomerulus. HE, magnification 180×
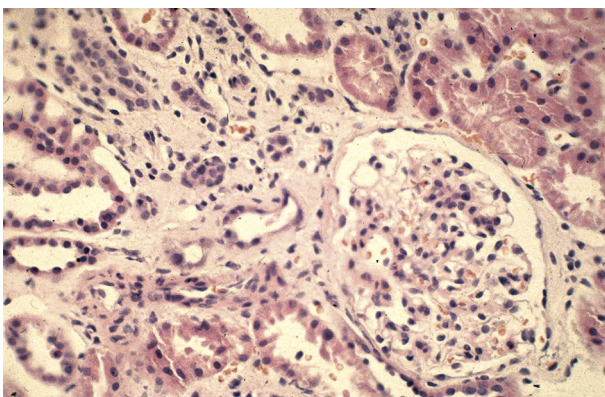

Fig. 3. FSGS NOS with small intensification. A vast focus of interstitial fibrosis in the neighborhood of the glomerulus. HE, magnification 180×
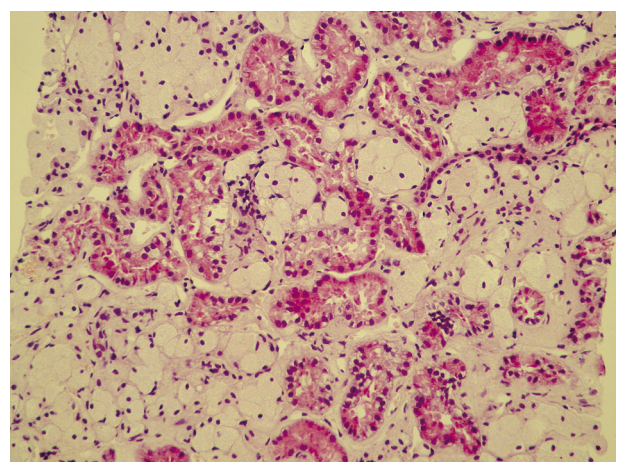

Fig. 4. Numerous foam cells in the interstitium. HE, magnification 180×

A group of 150 patients included 138 adults (87 males and 51 females) and 12 children (8 boys and 4 girls). The patient age in the adult group ranged from 19 to 77 years. Most of the children (6) were in the above 15 age group, and another 3 in the 10-14 age group (with one boy with an earlier onset of the disease and the first nephrotic syndrome episode at the age of 2). The group of youngest children included 2 boys aged 6 and 10, and a girl aged 9 at the time of biopsy, but with the disease onset 8 years before that.

The largest group of adults (58) included patients, in whom the disease started from proteinuria. The second largest group included 36 patients with initial symptoms of the nephrotic syndrome. Other groups consisted of 23 patients with symptoms of proteinuria and hypertension, 11 patients with proteinuria and erythrocyturia, 8 patients with proteinuria, erythrocyturia and hypertension.

In children, the disease started most commonly (in 7 cases) from a steroid-resistant nephrotic syndrome. Of other 2 cases, the disease started from proteinuria and erythrocyturia (with subsequent development of renal insufficiency in 1 child), isolated proteinuria in 2 children, isolated proteinuria, erythrocyturia and hypertension in 1 child.

The material for light microscopy examination was preserved in 7% neutral formalin. After standard preparation, paraffin-embedded tissues were stained with hematoxylin and eosin and impregnated with silver salts according to the Jone's method. PaS reaction was performed. In some cases, the paraffin-embedded tissues were stained according to Masson's trichrome method. Electron microscopy imaging was performed in 9 adults and 2 children. The portion of the punctat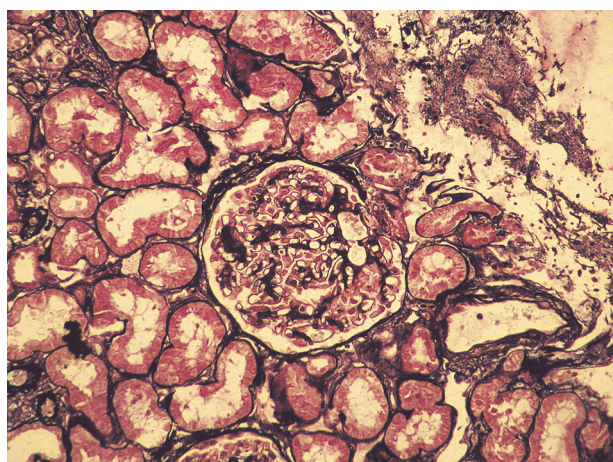e for electron microscopy examination was preserved in glu-taraldehyde, prepared by standard methods and embedded in EPON 812 epoxide resin. Semithin sections from Epon blocks were stained with toluidine blue and examined under light microscope. Ultrathin sections were evaluated under a Zeiss EM 900 or EM 10 electron microscope.

Immunofluorescence assays were performed in 90 adults and 16 children. Determination included immunoglobulin types A, G, M, complement fractions C3, C4, C1q, and fibrinogen. The assays were performed in the Department of Immunology of the Chair of Clinical Pathomorphology (currently the Chair of Immunology of the PUMS). Re-biopsies were performed in 22 adults and 8 children.

Histological section evaluation included the assessment of FSGS variant according to the classification proposed by D'Agati et al. [14]. The percentages of glomeruli with lesions specific to the particular FSGS variant were determined after elimination of completely sclerotized glomeruli.

Results

Adults

In the adult group, the disease most commonly started with proteinuria (in 58 cases). This was the case in 31 women and 27 men. The age of patients ranged from 19 to 74 years, without clear predominance of any particular decade.

Most patients (37) were diagnosed with FSGS NOS. The FSGS perihilar lesions were observed in 14 patients. The lesion type could not be determined in 7 patients. Besides FSGS NOS lesions, FSGH hilar

Fig. 5. FSGS NOS with small intensification. Increase in the number of matrices in different areas of the glomerulus. Impregnation with silver-containing salt acc. to Jones, magnification 180×
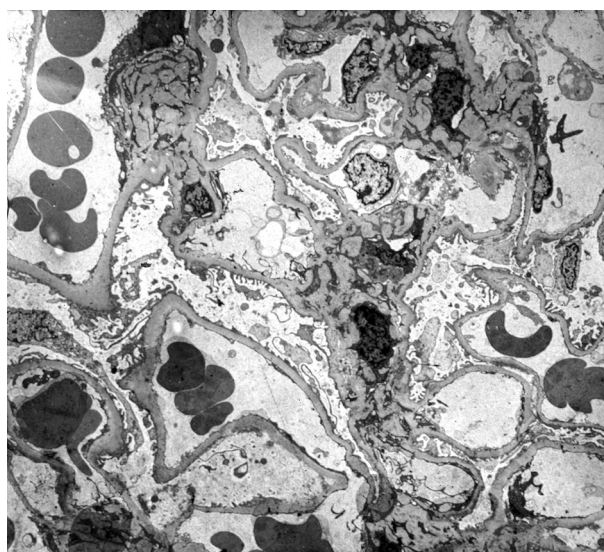

Fig. 6. Fragment of the glomerulus with insignificantly widened mesangial areas (due to matrix gain). Early stage of FSGS, magnification 4300×
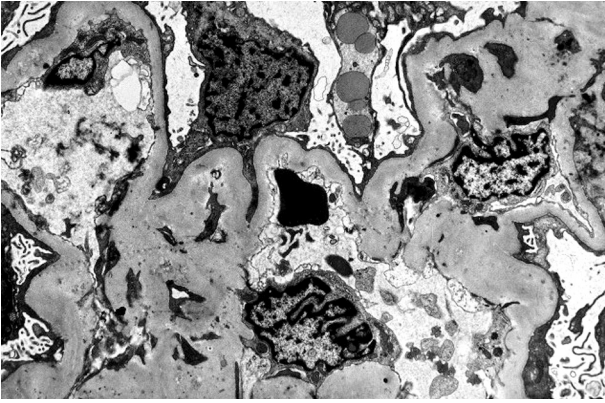
Fig. 7. Fragment of the glomerulus. Significant gain of matrix in mesangial areas. Only parts of cells are visible, magnification 7000×

Fig. 8. Fragment of the glomerulus. Numerous vacuoles in the cytoplasm of podocytes and endothelial cells, magnification 5600×

and FSGS tip lesions, as well as isolated completely sclerotic glomeruli were observed in these cases.

Completely sclerotic glomeruli were also observed in cases when evaluation of the disease variant posed no difficulties. They were present in 24 (out of 37) cases assessed to be FSGS NOS, and their number ranged from 1 out of 5 to 14 out of 25 glomeruli per punctate. In the perihilar variant group, completely sclerotic glomeruli were found in 8 patients. The number of completely sclerotic glomeruli ranged from 1 out of 6 to 12 out of 16 glomeruli per punctate.

Of note is the presence of perihilar lesions in 10 cases with predominant NOS lesions. The number of thus affected glomeruli ranged from 1 out of 9 to 3 out of 8 glomeruli per punctate.

The second largest group was a group of 36 patients with symptoms of nephrotic syndrome. The group included 24 men and 12 women aged from 21 to 77 years. Also in this group, no predominance of any particular age group was observed.

The FSGS NOS lesions were diagnosed in 31 individuals, and perihilar lesions were diagnosed in 7 individuals. In 1 case, the variant could not be determined due to the diversity of lesions. In that case, 4 out of 8 glomeruli present in the punctate were completely sclerotic, 2 contained NOS lesions and 2 contained perihilar lesions.

Completely sclerotic glomeruli were also present in cases which were definitely classified to a particular group. They could be found in 20 punctates with FSGS NOS lesions and in 1 case of perihilar lesions. The number of completely sclerotic glomeruli ranged from 1 out of 9 to 13 out of 18 glomeruli per punctate.

Perihilar lesions were also found in 8 cases with FSGS NOS lesion predominance. They were observed in 1 out of 10 to 2 out of 5 glomeruli per punctate.

The third largest group of 23 patients consisted of 18 men and 5 women aged from 19 to 69 years, presenting with symptoms of proteinuria and hypertension. Patients aged 19-29 years constituted the predominant
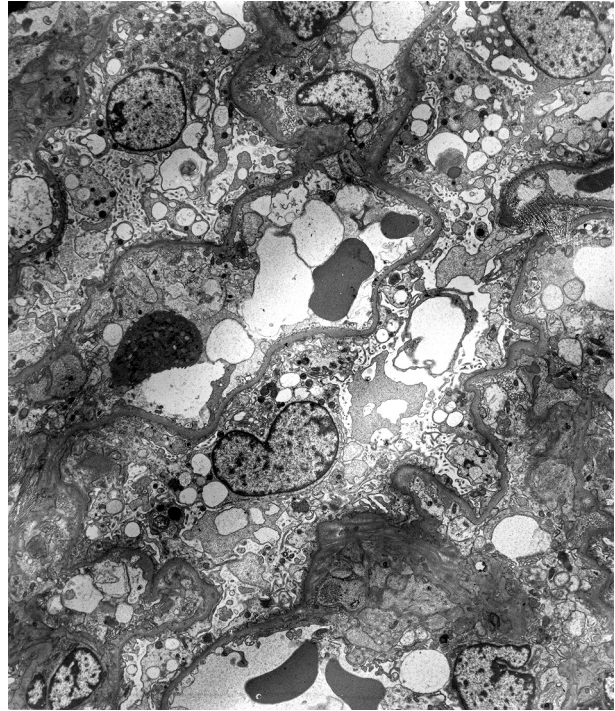
age subgroup within this group of patients. The next largest subgroup included patients aged 40-49 years and 30-39 years. The only elder patient was 69 years.

In this group, FSGS NOS lesions were observed in 22 individuals. In 13 of these 22 cases, completely sclerotic glomeruli were found. The number of these glomeruli ranged from of 1-2 out of 5 to 13 out of 17 glomeruli per punctate. In 1 patient, the type of lesions could not be definitely determined. Seven out of 11 glomeruli per punctate were completely sclerotic, and another 4 contained a moderately increased number of mesangial cells, with a perihilar lesion in one of these glomeruli. Isolated glomeruli with perihilar lesions were also observed in 6 cases with clear predominance of FSGS NOS lesions.

Another group of 11 patients consisted of 7 men and 4 women with symptoms of erythrocyturia and proteinuria. The youngest patient was 20 years old, and the oldest patient was 72 years old. The largest number of patients (5) were in the age group of 33-36 years.

The FSGS NOS lesions were found in 11 patients, with completely sclerotic glomeruli also found in 3 of these patients, ranging from 5 out of 8 to 5 out of 28 glomeruli per punctate.

In 6 patients with FSGS NOS lesions, perihilar lesions were also found, pertaining to isolated glomeruli. The only exception was the case in which perihilar lesions were found in 4 out of 30 glomeruli per punctate. Moreover, a distinct increase in mesangial cell and podocyte counts was observed in this case. The im-

munofluorescence assay did not confirm the initial suggestion of mesangial glomerulonephritis.

The group of 8 patients with proteinuria, erythrocyturia and hypertension consisted of 6 women and 2 men aged from 26 to 54 years. Also in this group, patients with FSGS NOS lesions were predominant. Among 9 patients with lesions of this type, isolated completely sclerotic glomeruli were found in 6 patients. In 8 patients, perihilar lesions were also present along with the predominant FSGS NOS lesions. The number of these lesions ranged from 4 out of 30 to 2 out of 7 glomeruli per punctate. Erythrocyturia was the first and only symptom in only 2 patients. The FSGS NOS lesions were found in both patients, a 64-year-old woman and a 31-year-old man. In the latter patient, perihilar lesions were also found in 4 out of 11 glomeruli per punctate. Completely sclerotic glomeruli were found in either of these two cases.

Children

The most common first symptom of the disease in this group of patients was steroid-resistant nephrotic syndrome, which affected 7 children. The disease started from proteinuria and erythrocyturia in 2 children. Isolated proteinuria was the first symptom in 2 children, proteinuria and hypertension in 1 child. In all 12 children, similar histological lesions of FSGS NOS type were found. They differed only in the severity of sclerotization. In 2 cases, additional perihilar lesions were observed in few glomeruli. The number of these lesions ranged from 1 out of 3 to 7 out of 17 glomeruli per punctate.

In all 12 cases, various degree of mesangial cell count increase was observed. In 6 cases, only isolated completely sclerotic glomeruli were observed.

In both groups – both adults and children – interstitial lesions were generally observed, such as fibrotic foci and lymphocytic infiltrates. The latter were usually scarce and of low intensity. The fibrotic foci differed significantly in size between individual cases, from tiny, macular foci to diffuse, merging areas. Their number and extent was usually, but not universally, associated with the severity of glomerular lesions. Sometimes distinct interstitial lesions were not accompanied by equally significant severity of glomerular lesions. Cells with foamy cytoplasm were found in the interstitium in one case in the children group and in 10 cases in the adult group.

In all cases, interstitial fibrosis was associated with varying degrees of tubular atrophy. Of note is the large percentage of nearly completely sclerotic glomeruli in both patient groups. No relationship between the presence of these sclerotic glomeruli and the duration of the disease was observed.

Immunofluorescence assays

Material from 110 adults and 12 children was sent for immunofluorescence assays. Twelve adult patient punctates contained no glomeruli, and no deposits were detected in 30 punctates. The remaining punctates contained deposits of IgM and C3, with 4 punctates containing also slight deposits of IgG. Deposits of IgM and C3 were found in all punctates collected from children.

Electron microscopy examinations

Material from as few as 11 patients (9 adults and 2 children) was sent for electron microscopy examination. Three patients (2 children and 1 adult) were diagnosed with FSGS only on the basis of this examination. Histological examination of these cases revealed only a slight increase in the quantity of mesangial matrix in isolated mesangial areas, which did not justify the diagnosis of sclerosis. On the other hand, the electron microscopy examinations revealed a significant increase in its quantity. In most mesangial areas, the matrix component was clearly dominant over the cellular component.

In 2 adults (1 with proteinuria, 1 with proteinuria and hypertension) presence of thin membranes was revealed in numerous capillary loops.

In all studied cases, attention was paid to the nature of cellular lesions. In 8 adults and all children, cytoplasmic vacuole changes were observed in endothelial cells. The vacuoles were present in large numbers and had large dimensions. Presence of vacuolar changes in the cytoplasm of podocytes was reported only in 5 adults and 1 child. In podocytes, the vacuoles were generally less numerous and small. The appearance of the vacuoles in both the endothelial cells and in the podocytes was quite diverse. Surrounded by a monolayered membrane, the vacuoles contained the material corresponding to proteins or proteoglycans, or, less frequently, lipids. Sometimes the vacuoles corresponded to the dilated intraplasmatic channels. In addition, quite numerous podocytes with light, swollen cytoplasm and diluted nuclear chromatin were found in 3 adults.

Rebiopsies

Rebiopsies were performed in 29 patients, 21 adults and 8 children. Rebiopsy was considered necessary mostly in 2 groups of patients, namely in individuals with proteinuria and nephrotic syndrome. In the first of these groups, rebiopsy was performed in 12 patients. In the group of patients with nephrotic syndrome, rebiopsy was performed in 7 adults and 7 children. In children, rebiopsies were performed in all patients in whom the syndrome was diagnosed. Other rebiopsies were performed in 2 adults and 1 child in whom proteinuria and hypertension was diagnosed.

Rebiopsies were performed 1 to 8 years after the first biopsy, in most patients 3-4 years after the first biopsy. Distinct features of progression were found in 19 adults and 3 children. No significant differences in

the nature and severity of lesions were observed in 1 adult and 5 children, which could be explained by the fact that only a year had passed between both biopsies. In another adult patient, severity of lesions in the rebiopsy was lower than in the first biopsy. In this case, rebiopsy was also performed one year after the first biopsy; moreover, a small amount of rather non-representative material was obtained in the rebiopsy.

Discussion

As mentioned in the introduction, interest in FSGS is increasing, both among clinicians and pathomorphologists. First of all, of importance is the growing number of patients with this type of lesions [25]. Hogg *et al.* [26] reported that in 1976, FSGS was significantly more frequently diagnosed in children (in 15% of patients with renal lesions) than in adults (2.5-4%). In 2006, the percentage of patients diagnosed with FSGS increased to 12.2-18.7%. We have found this percentage to be similar to the percentage of patients with this type of lesions in our research material. Most probably, besides the actual increase in the number of patients, more frequent early diagnoses of these lesions contribute to the observed increase.

Thomas [27] claims that as the number of data increases and as the new classification is being introduced, the role of pathomorphologist is on the increase and one might expect further progress in the morphological diagnostics. However, it should be highlighted that, as also mentioned in the introduction, diagnosis of FSGS is often associated with difficulties. This is particularly true at early stages of lesion development, when the increase in the quantity of mesangial matrix is small and undetectable in light microscopy examination. Although Jones silver salt impregnation, which makes the matrix well visible, may be of some help here, the results of electron microscopy would be most reliable. In the presented material, FSGS was diagnosed solely on the basis of ultrastructural examination in 3 cases. However, it must be noted that we could obtain the material secured for this examination only from 16 patients. It is hard to assess how the number of glomerulosclerosis would increase should a portion of punctate be secured for electron microscopy in each renal biopsy. Except for revealing the increase in matrix quantity, these examinations allowed for determination of the nature of vacuolar changes in podocytes and endothelial cells. These were also discussed in one of our previous papers [28]. We must note that the results of our studies at that time did not confirm observations made by other authors [29, 30], who attribute a prognostic value to the presence of vacuoles. In another of our previous papers [31], we have presented the results of morphometric examinations and their usefulness in differential diagnosis of submicroscopic glomerulonephritis, mesangial glomerulonephritis and FSGS.

We have also shown the usefulness of these examinations in early determination of the risk of sclerotization in the case of mesangial glomerulonephritis. We emphasize that this was the first paper regarding morphometric examinations of electron microscopy materials. We are confident that as many as possible of these examinations should be performed. Unfortunately, the biopsy materials obtained from adults are in most cases not secured for this purpose (for economic reasons).

Much attention is focused in the literature on the enlargement in glomerular dimensions as an exponent of the risk of sclerotization. In our material, the enlargement of glomeruli was generally observed in small numbers of glomeruli with simultaneous presence of normal size, or even small glomeruli in the same punctate. However, it must be noted that the presence of large glomeruli (regardless of their number) is most commonly observed in cases of FSGS.

Identification of interstitial fibrotic foci could be of help in relation to FSGS diagnosis. Sometimes they are discreet and more easily detected in preparations stained according to Masson's trichrome method. The presence of these lesions, and particularly their incommensurability with the severity of glomerular lesions, often suggests further diagnostic procedures. Although non-decisive, they suggest a possibility of early-stage FSGS.

It is often difficult to diagnose FSGS types other than the most common classic FSGS NOS. Therefore, the authors of the classification [14] recommend examining at least 15 serial sections. Unfortunately, the amount of the material received is small and it is impossible to obtain such a number of sections, or there are no glomeruli in deeper sections. The principle for identification of particular types is also subject to discussion. According to the proposal set forth by the authors of the classification, at least 50% of glomeruli present in the punctate should have the features of a particular type. A question arises, however, what should be done in cases when most of the glomeruli is completely sclerotic while there are different types of lesions in the remaining, less damaged glomeruli. In our research material, in such cases we encountered glomeruli with FSGS NOS and perihilar-type lesions. Doubts also arise in cases where most glomeruli present in the punctate are completely sclerotic, and the remaining glomeruli have no detectable lesions.

Finally, it is questionable whether determination of particular types by the clinicians is really indispensable. This question has remained essentially unanswered by the classification authors. It was only ascertained [14, 32-34] that the tip variant is associated with better prognoses than the other variants, while the prognoses are worst in the case of the collapsing variant. However, it is not known whether the treatment should be variant-dependent. In our material, FSGS NOS was the

most commonly diagnosed variant, followed by the perihilar variant. The tip variant was diagnosed in only one case. We have encountered no case of the collapsing variant.

Most authors report that FSGS is associated with the nephrotic syndrome or isolated proteinuria, sometimes accompanied by hypertension. Only few researchers (we quote after [17]) find that erythrocyturia is not uncommon, especially in children.

In our material, erythrocyturia was observed in 23 adults (including 2 cases of isolated erythrocyturia) and in 2 children. No other exponents of glomerulopathy were found in this group. Considering the above, we believe that FSGS does not have to be associated only with proteinuria or nephrotic syndrome. Erythrocyturia was also observed in another our group of children, described in a previous paper [9].

Conclusions

1. In the presented material, focal segmental glomerulosclerosis was most often associated with symptoms of proteinuria or nephrotic syndrome. However, the diversity of symptoms was fairly common. Proteinuria was accompanied by hematocyturia and hypertension; isolated hematocyturia was also observed. Thus, the clinical picture is not always unambiguous.
2. While cases characterized by FSGS NOS lesions are predominant, of note is a relatively populous group of cases in which FSGS NOS lesions are accompanied by FSGS hilar and/or FSGS tip lesions. Such combination of lesions markedly hinders determination of the lesion type.
3. Of note is also incidence of completely sclerotized glomeruli, often with simultaneous presence of glomeruli with low lesion intensity. The presence of completely sclerotized glomeruli, even relatively abundant, is not clearly associated with the duration of the disease.

References

1. Ichikawa I, Fogo A. Focal segmental glomerulosclerosis. Pediatr Nephrol 1996; 10: 374-391.
2. Koushik R, Matas AJ. Focal segmental glomerular sclerosis in kidney allograft recipients: an evidence-based approach. Transplant Rev 2005; 19: 78-87.
3. Fine RN. Reccurence of nephrotic syndrome/focal segmental glomerulosclerosis following renal transplantation in children. Pediatr Nephrol 2007; 22: 496-502.
4. Ingulli E, Singh A, Baqi N, et al. Aggressive, long-term cyclosporine therapy for steroid-resistant focal segmental glomerulosclerosis. J Am Soc Nephrol 1995; 5: 1820-1825.
5. Mendoza SA, Reznik VM, Griswold WR, et al. Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agents. Pediatr Nephrol 1990; 4: 303-307.
6. O'Regan S, Murphy GF, Robitaille P, et al. Decreased hospitalization and increased height velocity in focal segmental glomerulosclerosis responsive to cyclosporine A. Child Nephrol Urol 1991; 19: 185-189.
7. Tune BM, Kirpekar R, Sibley RK, et al. Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: a long term follow-up. Clin Nephrol 1995; 43: 84-88.
8. Stirling CM. Focal segmental glomerulosclerosis – does treatment work? Nephron Clin Pract 2006; 104: 83-84.
9. Salwa-Żurawska W, Bortkiewicz E, Turczuk-Bierła I, Maciejewski J. Focal segmental glomerulosclerosis in children. Pol J Pathol 1992; 43: 45-50.
10. Fogo A, Hawkins EP, Berry PL, et al. Glomerular hypertrophy in minimal change disease predicts subsequent progression to focal glomerular sclerosis. Kidney Int 1990; 38: 115-123.
11. Silva FG, Hogg RJ. Minimal change nephrotic syndrome – focal sclerosis complex (including IgM nephropathy and diffuse mesangial hypercellularity). In: Renal pathology with clinical and functional correlations. Tisher CC, Brenner BM (eds.). JB Lippncott Comp, Philadelphia 1989; 265-339.
12. Hayslett JP, Krassner LS, Bensch FG, et al. Progression of "lipoid nephrosis" to renal insufficiency. N Engl J Med 1969; 281: 181.
13. Newman WJ, Tisher CC, Mc Coy RC. Focal glomerular sclerosis: Contrastin clinical patterns in children and adults. Medicine 1976; 55: 67-87.
14. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis 2004; 43: 368-382.
15. Fogo AB, Kashgarian M. Minimal change disease and focal segmental glomerulosclerosis. In: Diagnostic atlas of renal pathology. Fogo AB, Kashgarian M (eds.). Elsevier Saunders 2005; 13-44.
16. Lee HS, Kim TS. A morphometric study of preeclamptic nephropathy with focal segmental glomerulosclerosis. Clin Nephr 1995; 44: 13-24.
17. Schwartz MM. Focal segmental glomerulosclerosis. In: Heptinstall's pathology of the kidney. Jennette JC, Olson JL, Schwartz MM, Silva FG (eds.). Lippincott Williams and Wilkins 2006; 155-204.
18. Kihara I, Tsuchida S, Yaoita E, et al. Podocyte detachment and epithelial cell reaction in focal segmental glomerulosclerosis with cellular variants. Kidney Int 1997; 52: 171-176.
19. Shui HA, Ka SM, Yang SM, et al. Osteopontin as an injury marker expressing in epithelial hyperplasia lesions helpful in prognosis of focal segmental glomerulosclerosis. Translat Res 2007; 150: 216-222.
20. Hara M, Yanagihara T, Kihara I. Urinary podocytes in primary focal sagmental glomerulosclerosis. Nephron 2001; 89: 342-347.
21. Woroniecki RP, Kopp JB. Genetics of focal segmental glomerulosclerosis. Pediatr Nephrol 2007; 22: 638-644.
22. Tsukaguchi H, Sudhakar A, Le TC, et al. NPHS2 mutations in late-onset focal segmental glomerulosclerosis: R229Q is a common disease-associated allele. J Clin Invest 2002; 110: 1659-1666.
23. Tonna SJ, Needham A, Polu K, et al. NPHS2 variation in focal segmental glomerulosclerosis. BMC Nephrology 2008; 9: 13.
24. Voskarides K, Damianou L, Neocleous V, et al. COL4A3/COL4A4 mutations producing focal segmental glomerulosclerosis and renal failure in thin basement membrane nephropathy. Am J Soc Nephrol 2007; 18: 3004-3016.
25. Reidy K, Kaskel FJ. Pathophysiology of focal segmental glomerulosclerosis. Pediatr Nephrol 2007; 22: 350-354.
26. Hogg R, Middleton J, Vehaskari VM. Focal segmental glomerulosclerosis – epidemiology aspects in children and adults. Pediatr Nephrol 2007; 22: 183-186.
27. Thomas DB. Focal segmental glomerulosclerosis. Arch Pathol Lab Med 2009; 133: 217-223.
28. Salwa-Zurawska W, Woźniak A, Biczysko W, et al. Is vacualisation of podocytes and glomerular endothelial cells of prognostic value with respekt to FSGS? Pol J Pathol 1998; 49: 165-174.

29. Chiang ML, Hawkins EP, Berry PL, et al. Diagnostic and prognostic significance of glomerular epithelial cell vacualisation and podocyte effacement in children with minimal lesion nephrotic syndrome and focal segmental glomerulosclerosis: an ultrastructural study. Clin Nephrol 1988; 30: 8-14.

30. Yoshikawa N, Ito H, Akamatsu R, et al. Glomerular podocyte vacualisation in focal segmental glomerulosclerosis. Arch Pathol Lab Med 1986; 110: 394-398.

31. Woźniak A, Kaczmarek E, Salwa-Zurawska W, et al. Morphometric analysis in the diagnosis and differentiation of certain glomerulopathies (MCD, GNMes, FSG). Pol J Pathol 1994; 45: 187-193.

32. Deegens JK, Steenbergen EJ, Borm GF, Wetzels JF. Pathological variants of focal segmental glomerulosclerosis in an adult Dutch population – epidemiology and outcome. Nephrol Dial Transplant 2008; 23: 186-192.

33. Valeri A, Barisoni L, Appel GB, et al. Idiopathic collapsing focal segmental glomerulosclerosis: a clinicopathologic study. Kidney Int 1996; 50: 1734-1746.

34. Meyrier AY. Collapsing glomerulopathy: expanding interest in a shrinking tuft. Am J Kidney Dis 1999; 33: 801-803.

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