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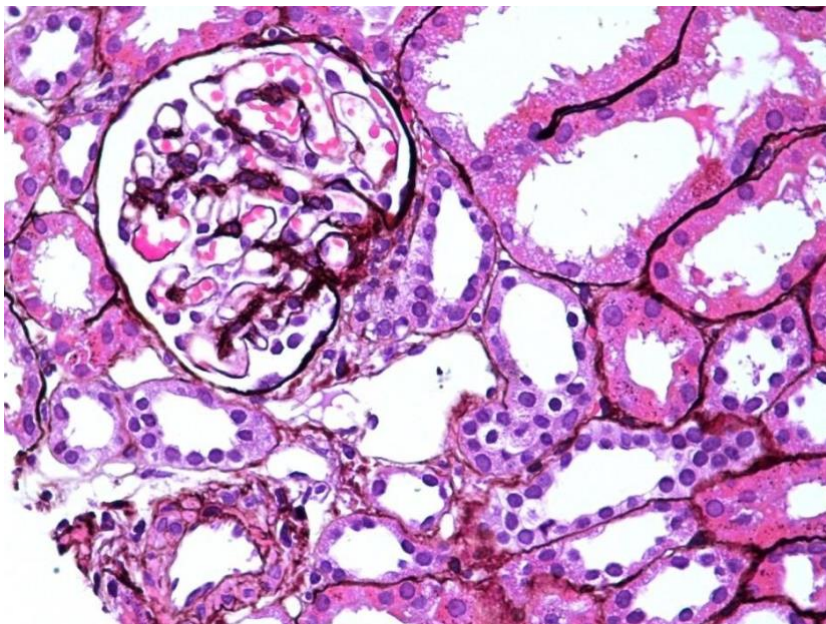
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Normal Renal Pathology

Case 1:



Single glomerulus seen on on light microscopy. Normal glomerulus with surrounding parenchyma is unaffected. The tubules normal placed as back-to-back and a single normal arteriole is also seen. This biopsy can be labelled as a normal biopsy or a patient with Minimal Change Disease. (Jones' methenamine silver stain, ×400).

Differential diagnosis of minor glomerular abnormalities on light microscopy (LM).

- Minimal change disease (MCD)
- Early-stage focal segmental glomerulosclerosis (FSGS)
- Lupus nephritis class I
- Prespike membranous GN
- IgA nephropathy
- IgM nephropathy
- Early-stage Amyloidosis

- Alport' syndrome
- Thin basement membrane disease

Case 2.

Renal biopsy done on a 17-year-old male with steroid resistant nephrotic syndrome (SRNS), hypertension and hematuria.

Figure 1 (Periodic acid-Schiff, ×200) shows a low-power view of an area of renal biopsy from the above patient with one glomerulus which is showing a segmental lesion. Tubular atrophy is seen with associated interstitial fibrosis and inflammation. A comment on focal vs. diffuse nature of the lesion cannot be made as only one glomerulus is included.

Figure 2 (Periodic acid-Schiff, ×400) shows high-power view of the same glomerulus has segmental sclerosis and hyalinosis and clear adhesion formation is observed with Bowman' s capsule. In sclerotic area there is loss of capillary lumina; as a result of which, the affected glomerular tuft assumes a solid appearance.

Figure 3 (Jones methenamine silver, ×100) shows two relatively normal looking glomeruli, one globally sclerosed glomerulus, and mild patchy tubular atrophy. The large interlobar size artery is showing mild fibro intimal thickening.

Figure 4 (Jones methenamine silver, ×400) shows high-power view of a similar glomerulus as shown in Figure 2, but the stain is different. The distinction between hyalinosis and sclerosis is obvious by noting that sclerotic areas stain black with silver stain whereas hyaline deposits do not stain black with this stain. The Juxta-hilar location is usually seen as the common site for the origin of segmental scarring. The other part of the glomerulus is normal.

Because the distribution of lesions in this category is focal and segmental, it can be easily missed if not looked for carefully and during the early stages of the disease, when only a small proportion of glomeruli may be involved. In these situations, The presence of tubular atrophy and vasculopathy should point towards the possibility of finding segmental scars on serial sections.

Focal segmental glomerular lesions are characterized by: the focal distribution (affecting less than 50% of glomeruli) and segmental (affecting only part of the involved glomerulus) involvement on light microscopic (LM) level. Nature of the lesion can be necrotizing, inflammatory or sclerotic. Thus, focal segmental lesions are broadly divided into focal segmental glomerulosclerosis (FSGS) and focal segmental glomerulonephritis (FGN) types. It is important to make a distinction among these, as both usually have different clinical presentation and different prognostic implications. In this particular case, the lesions belong to FSGS category, as discussed below.

Figure 1

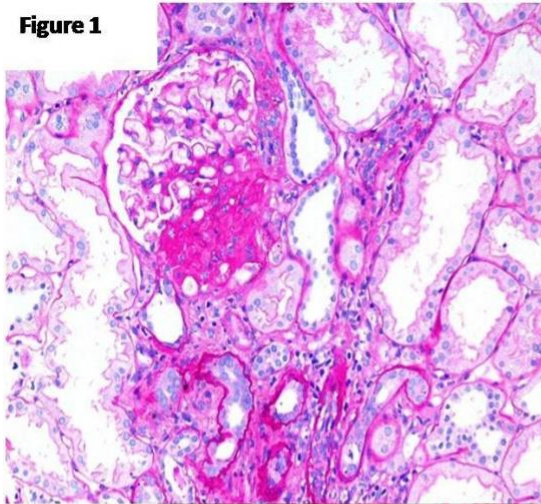


Figure 2

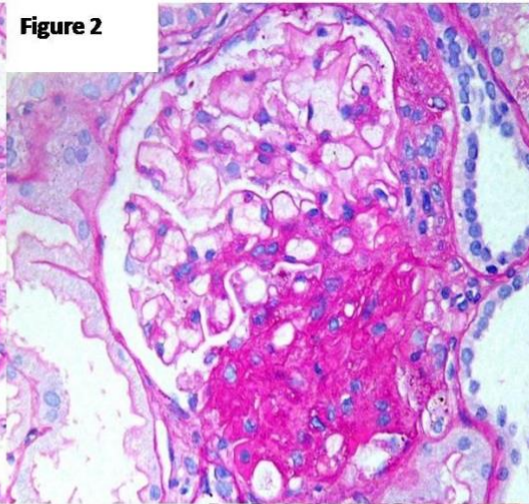


Figure 3



Figure 4



The characteristic lesion of FSGS consists of segmental sclerosis and hyalinosis and the sclerotic material comprises of increased mesangial matrix and the collapsed and condensed glomerular basement membranes (GBMs) and has a non-homogeneous, fibrillary appearance. It stains pink with eosin, magenta with Periodic acid-Schiff (PAS), green with trichrome stain, and black with silver stain. The affected segment may or may not show areas of hyalinosis, intracapillary foam cells and adhesion formation with Bowman's capsule. The non-sclerotic segments of the involved glomeruli may show either minor changes or mild to moderate mesangial proliferation. Various forms of arteriosclerosis, tubular atrophy and interstitial inflammation also accompany.

Focal/segmental glomerular lesions-III

Case 4

Here are two more representative images from a renal biopsy done on case 2 that was discussed previously in September issue of this journal (vol. 1, issue 3). So the case history will not be repeated here.

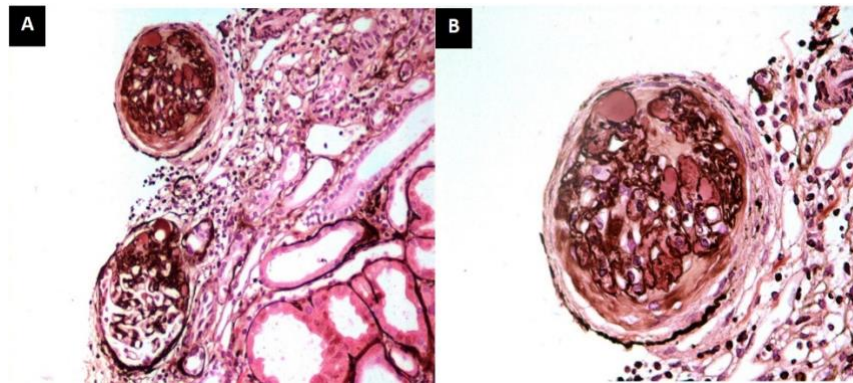


Figure A

(Jones methenamine silver, $\times 100$) shows a low-power view of one representative area of renal biopsy from the above patient with two glomeruli surrounded by a patch of tubular atrophy and interstitial inflammation and fibrosis. The lower glomerulus is showing segmental pathology, while the upper one global involvement (focal global glomerulosclerosis). At this magnification and on this special stain, both glomeruli are showing evidence of hyalinosis, to be discussed in detail below. This finding implies that origin of global glomerulosclerosis is probably secondary to focal segmental glomerulosclerosis (FSGS).

Figure B

(Jones methenamine silver, $\times 200$) shows medium-power view of the upper glomerulus in Figure 1, which is grossly abnormal in appearance, and shows global glomerulosclerosis. It is surrounded by a patch of tubular atrophy associated with interstitial sclerosis and mild interstitial inflammation. Global glomerulosclerosis is the end-point lesion of glomerular injury from a variety of causes, be they immune mediated or non-immune mediated. The presence of foci of hyaline deposition (hyalinosis) in this glomerulus suggests that this might represent advanced stage of a process that most likely began as FSGS.

DISCUSSION

Focal and segmental lesions of glomerular sclerosis evolve into diffuse and global lesions with advancement of the disease process. The degree of global glomerulosclerosis is variable and depends on disease severity, the timing of the biopsy, and the rate of disease progression. The finding of only global glomerulosclerosis, without segmental lesions, is nonspecific and increases with age, reflecting concurrent arterionephrosclerosis related to senescence and/or hypertension. There are many other causes of global sclerosis as well. The global glomerulosclerosis can be broadly categorized as glomerulopathic (solidified), vasculopathic (obsolescent), or involutional (microglomeruli) types. The globally sclerosed glomerulus shown in the above case represents glomerulopathic type of global sclerosis. Glomerulopathic sclerosis is characterized by a solidified, non-retracted glomerular tuft (glomerular size remains normal) with often recognizable tuft adhesions with Bowman's capsule, splitting of Bowman's capsule and without the homogeneous collagenous matrix in Bowman's space. It has been suggested that global sclerosis may also occur without renal disease (i.e., physiological) as part of a normal damage and repair process. In fact, globally sclerosed glomeruli have been found in children below the age of 2 years. In adults, a formula has been suggested for normal percent of global sclerosis of up to half the patient's age, minus 10, for example, up to 30% by age 80.

Global glomerulosclerosis:

1. Glomerulopathic (solidified)
2. Vasculopathic (obsolescent)
3. Involutional (microglomeruli)

Of note, global glomerulosclerosis is always accompanied by both periglomerular and tubulo-interstitial fibrosis. Recently, it has been proposed that misdirected filtration may serve as a mechanism by which glomerulosclerosis leads to periglomerular and tubulo-interstitial fibrosis.

In this particular case, there is evidence that the global glomerulosclerosis is the end-result of FSGS lesion, as is apparent in Figure 1. Globally sclerosis may coexist with segmental lesions at the time of initial biopsy. However, the proportion of global sclerosis increases with the passage of time. In the absence of such evidence, it may be difficult or even impossible to discern the cause of global sclerosis. The presence of hyalinosis in globally sclerotic glomeruli suggests an origin from FSGS, but there are exceptions.

Expected percentage of Glomerulosclerosis:

Half the patient's age, minus 10

e.g.: $80 \text{ years} / 2 = 40 - 10 = 30\%$

TAKE HOME POINTS

- There are several types of global glomerulosclerosis and pathologists should familiarize with these in order to make correct interpretation of the underlying cause.
- The presence of global sclerosis, on its own, even if focally distributed, is not compatible with a diagnosis of FSGS.
- The presence of tuft adhesions and hyalinosis and lack of intra-Bowman's sclerosis favor glomerulopathic causation of global glomerulosclerosis and suggest its origin from FSGS.

Focal/segmental glomerular lesions-II

Case 3

Here is a representative image from a renal biopsy done on a 12-year-old male with steroid dependant nephrotic syndrome (SDNS) associated with microscopic haematuria. No systemic diseases. No family history of renal disease. Relevant viral serology was negative.

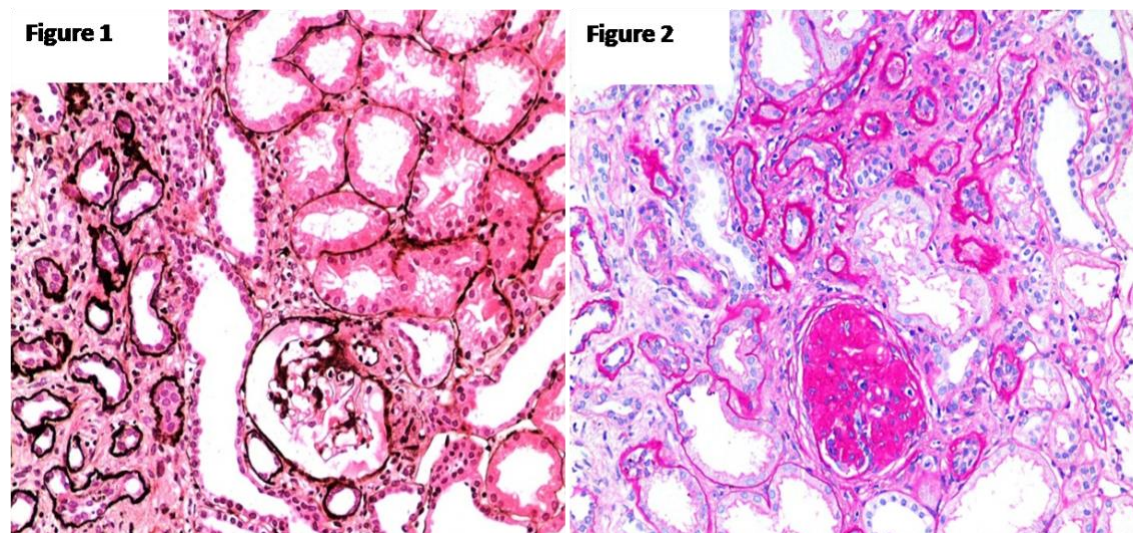


Figure 1 (Jones methenamine silver (JMS), $\times 200$) shows a medium-power view of one representative area of renal biopsy from the above patient with one glomerulus which is showing minor changes on light microscopy (LM). No segmental pathology is seen in this glomerulus. However, there is a patch of tubular atrophy on one side of the field associated with interstitial fibrosis and inflammation. The later finding implies that there is a glomerulus in the vicinity of this focus which has probably not been sampled in this biopsy. However, one thing is definite that this case does not belong to minimal change disease (MCD). In such situations, where even serial sections have not been successful in identify a glomerular pathology, a comment should be included at the end of biopsy report that the possibility of focal segmental glomerulosclerosis (FSGS) can not be entirely excluded.

Figure 2 (Periodic acid-Schiff (PAS), $\times 200$) shows medium-power view of another representative area of biopsy from the same patient. Here a glomerulus is included and is grossly abnormal in appearance, showing global glomerulosclerosis. There is no obvious morphological evidence of podocytopathy in this case. This is also a non-specific finding and on its own is not sufficient to diagnose a case as FSGS. It is surrounded by a patch of tubular atrophy associated with interstitial sclerosis and mild interstitial inflammation. Sometimes, one comes across only these findings in the whole biopsy material and no segmental lesion is identified. In such situations, again a comment on the possibility of unsampled FSGS should be added in the report, provided other ancillary techniques do not support any other diagnosis.

DISCUSSION

The main clinical presentation of this case, as in previous two cases, is with idiopathic nephrotic syndrome (NS), but the disease in this case requires continued use of steroids to remain in remission, hence the term steroid-dependent NS (SDNS). As described in case 2, the therapeutic response to steroids represents one of the important prognostic factors for pediatric NS and is often used to classify idiopathic NS in this age group. The age of the child is at borderline of young children and adolescents and he has microscopic haematuria. As noted in case 2, these features may be seen in some cases of minimal change disease (MCD), but the chances of finding more ominous forms of histopathological lesions increase with these additional clinical features and with increasing age.

Regarding the morphological features in this biopsy, both the main findings, i.e., focal tubular atrophy and global glomerulosclerosis, are nonspecific histological features and can be found in a variety of renal diseases, and in themselves, are not sufficient to positively diagnose a case as FSGS. However, their presence in the biopsy should alert the pathologist to the possibility of finding the diagnostic segmental glomerular lesions of FSGS. The likelihood of finding the later depends on both the proportion of glomeruli affected by the disease and by the sample size, and FSGS lesions may be missed in small biopsy samples. These can also be

missed in early stages of disease if only superficial cortex is included in the biopsy, or in advanced stages, when majority of glomeruli show global glomerulosclerosis. However, it should be noted that the finding of even a single glomerulus with segmental scar is sufficient for the conclusive diagnosis of FSGS.

Therefore, additional tissue sections should be performed if there is a high clinical suspicion of FSGS, such as poor response to steroids, hypertension, and hematuria. In addition, if the biopsy reveals global glomerulosclerosis or focal tubular atrophy and interstitial fibrosis without segmental sclerosing glomerular lesions, a more exhaustive search for unsampled FSGS should be made by serial sectioning the whole renal biopsy. In some cases, the portions of the biopsy allocated for immunofluorescence (IF) and electron microscopy may be processed and examined by LM for identifying possible FSGS lesions. Other surrogate pathological features of unsampled FSGS on renal biopsy include glomerulomegaly, diffuse mesangial hypercellularity and mesangial positivity of IgM in either diffuse or segmental distribution on IF microscopy. The presence of these features should also raise the index of suspicion for the diagnosis of FSGS.

If all the above attempts fail to find the diagnostic lesions of FSGS, then a comment on the adequacy of biopsy, particularly the inclusion or otherwise of corticomedullary junction in the biopsy, should be included in the biopsy report and the possibility of FSGS should be raised.

Take home points

- Sampling error is always a problem in a needle biopsy of the kidney in focal diseases.
- The presence of focal tubular atrophy and interstitial sclerosis should alert the pathologist to look carefully for diagnostic features of FSGS by serial sections.
- If no incontrovertible evidence of FSGS is found, even after examining multiple serial sections, a comment should be added in the final report that the possibility of FSGS can not be entirely excluded.
- The presence of global glomerulosclerosis, on its own, is not diagnostic of FSGS.

Focal Segmental/global glomerular lesions-III

Case 5

Here is a representative image from a renal biopsy done on a 12-year-old male with steroid dependant nephrotic syndrome (SDNS) associated with microscopic haematuria. No systemic diseases. No family history of renal disease. Relevant viral serology was negative.

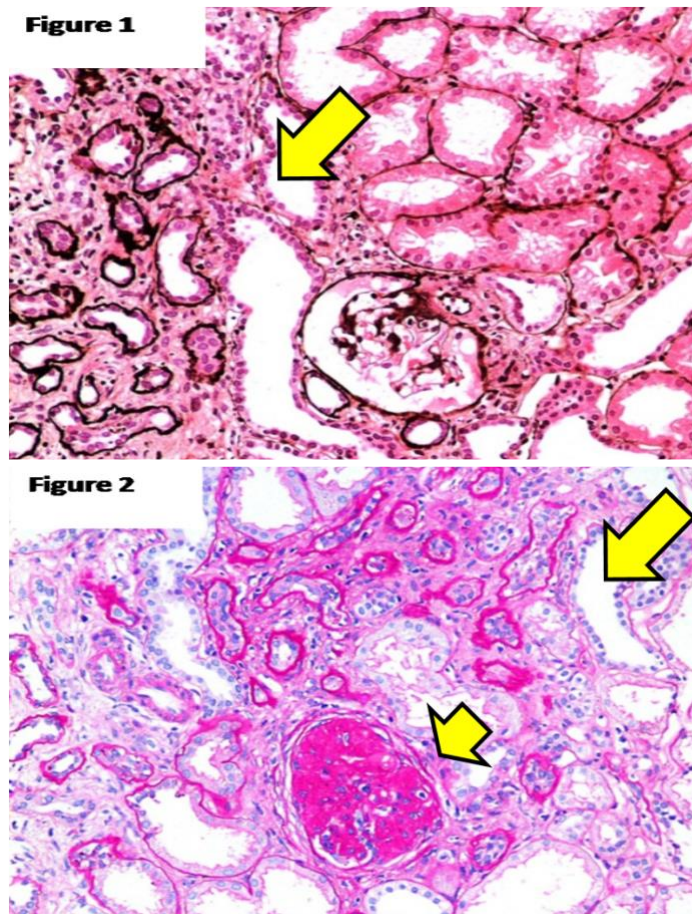


Figure 1 (Jones methenamine silver (JMS), $\times 200$) shows a medium-power view of one representative area of renal biopsy from the above patient with one glomerulus which is showing minor changes on light microscopy (LM). No segmental pathology is seen in this glomerulus. However, there is a patch of tubular atrophy on one side of the field associated with interstitial fibrosis and inflammation (arrow). The latter finding implies that there is a glomerulus in the vicinity of this focus which has probably not been sampled in this biopsy. However, one thing is definite that this case does not belong to minimal change disease (MCD). In such situations, where even serial sections have not been successful in identifying a glomerular pathology, a comment should be included at the end of the biopsy report that the possibility of focal segmental glomerulosclerosis (FSGS) can not be entirely excluded.

Figure 2 (Periodic acid-Schiff (PAS), $\times 200$) shows medium-power view of another representative area of biopsy from the same patient. Here a glomerulus is included and is grossly abnormal in appearance, showing global glomerulosclerosis (short arrow). There is no obvious morphological evidence of podocytopathy in this case. This is also a non-specific finding and on its own is not sufficient to diagnose a case as FSGS. It is surrounded by a patch of tubular atrophy associated with interstitial sclerosis and mild interstitial inflammation (Long arrow). Sometimes, one comes across only these findings in the whole biopsy material and no segmental lesion is identified. In such situations, again a comment on the possibility of unsampled FSGS should be added in the report, provided other ancillary techniques do not support any other diagnosis.

DISCUSSION

The main clinical presentation of this case, as in previous two cases, is with idiopathic nephrotic syndrome (NS), but the disease in this case requires continued use of steroids to remain in remission, hence the term steroid-dependent NS (SDNS). As described in case 2, the therapeutic response to steroids represents one of

the important prognostic factors for pediatric NS and is often used to classify idiopathic NS in this age group. The age of the child is at borderline of young children and adolescents and he has microscopic haematuria. As noted in case 2, these features may be seen in some cases of minimal change disease (MCD), but the chances of finding more ominous forms of histopathological lesions increase with these additional clinical features and with increasing age.

Regarding the morphological features in this biopsy, both the main findings, i.e., focal tubular atrophy and global glomerulosclerosis, are nonspecific histological features and can be found in a variety of renal diseases, and in themselves, are not sufficient to positively diagnose a case as FSGS. However, their presence in the biopsy should alert the pathologist to the possibility of finding the diagnostic segmental glomerular lesions of FSGS. The likelihood of finding the later depends on both the proportion of glomeruli affected by the disease and by the sample size, and FSGS lesions may be missed in small biopsy samples. These can also be missed in early stages of disease if only superficial cortex is included in the biopsy, or in advanced stages, when majority of glomeruli show global glomerulosclerosis. However, it should be noted that the finding of even a single glomerulus with segmental scar is sufficient for the conclusive diagnosis of FSGS.

Therefore, additional tissue sections should be performed if there is a high clinical suspicion of FSGS, such as poor response to steroids, hypertension, and hematuria. In addition, if the biopsy reveals global glomerulosclerosis or focal tubular atrophy and interstitial fibrosis without segmental sclerosing glomerular lesions, a more exhaustive search for unsampled FSGS should be made by serial sectioning the whole renal biopsy. In some cases, the portions of the biopsy allocated for immunofluorescence (IF) and electron microscopy may be processed and examined by LM for identifying possible FSGS lesions. Other surrogate pathological features of unsampled FSGS on renal biopsy include glomerulomegaly, diffuse mesangial hypercellularity and mesangial positivity of IgM in either diffuse or segmental distribution on IF microscopy. The presence of these features should also raise the index of suspicion for the diagnosis of FSGS.

If all the above attempts fail to find the diagnostic lesions of FSGS, then a comment on the adequacy of biopsy, particularly the inclusion or otherwise of corticomedullary junction in the biopsy, should be included in the biopsy report and the possibility of FSGS should be raised.

TAKE HOME POINTS

- Sampling error is always a problem in a needle biopsy of the kidney in focal diseases.
- The presence of focal tubular atrophy and interstitial sclerosis should alert the pathologist to look carefully for diagnostic features of FSGS by serial sections.
- If no incontrovertible evidence of FSGS is found, even after examining multiple serial sections, a comment should be added in the final report that the possibility of FSGS can not be entirely excluded.
- The presence of global glomerulosclerosis, on its own, is not diagnostic of FSGS.

Focal/segmental glomerular lesions-IV Case 5.

Here is a representative image from a renal biopsy done on a 55-year-old male with long-standing hypertension and non-nephrotic range proteinuria. Relevant viral serology was negative.

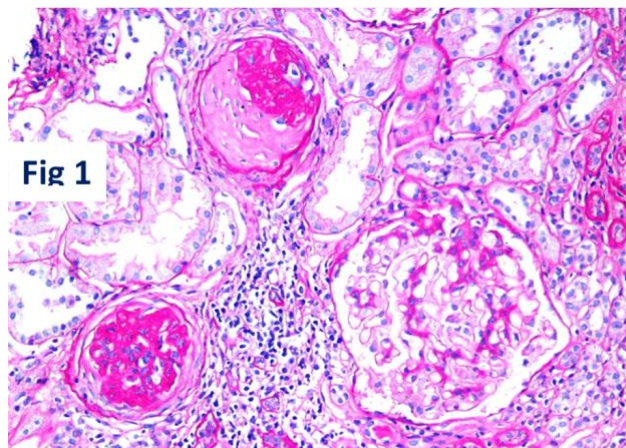


Figure 1 (Periodic acid Schiff, $\times 100$) shows a medium-power view of one representative area of renal biopsy from the above patient with one glomerulus which is showing minor changes on light microscopy (LM). No segmental pathology is seen in this glomerulus. However, remaining two glomeruli are solidified and non-functional. Note the size of these globally sclerosed glomeruli as compared with the normal glomerulus in the field. Both globally sclerosed glomeruli show retracted glomerular tufts and the Bowman's space of both is filled by pale pink, lightly staining, hyalinized collagenous material. This is characteristic of the vasculopathic type of global glomerulosclerosis. In addition, there is periglomerular fibrosis around the globally sclerosed glomeruli, surrounded in turn by patch of tubular atrophy associated with interstitial inflammation and fibrosis. Note that no sizeable vessel is included.

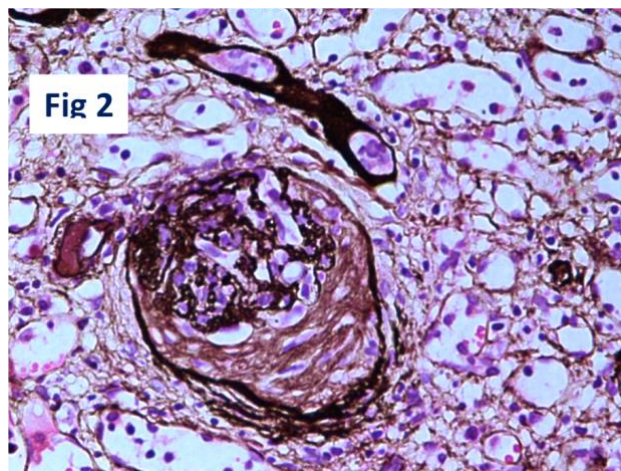


Figure 2 (Jones methanamine silver, $\times 200$) shows medium-power view of a glomerulus showing global glomerulosclerosis of the vasculopathic type. Note the retracted glomerular tuft and the surrounding Bowman's space filled with bland fibrous tissue, characteristic of vasculopathic nature of the glomerular consolidation. There is periglomerular fibrosis associated with moderate to severe tubular atrophy (in this field) and interstitial inflammation and fibrosis. One arteriole at 9'O clock position shows arteriolar hyalinosis.

DISCUSSION

There are two main types and underlying pathways of development of global glomerulosclerosis.

Types of Global Glomerulosclerosis
1:Glomerulopathic
2:vasculopathic

In the previous cases, we have discussed the glomerulopathic type of global glomerulosclerosis, which is characterized by solidified but non-retracted glomerular tuft with recognizable tuft adhesions associated with or without foci of hyalinosis. In this case, we discuss the other main type of global glomerulosclerosis, i.e., vasculopathic type.

The later is characterized by a retracted glomerular tuft, without recognizable tuft adhesions, surrounded by a hypocellular, pinkish, hyalinized collagenous matrix in the dilated Bowman's space. The later is highlighted on PAS and silver stains as shown in Figures 1 and 2 in this case. The above case was diagnosed as benign nephrosclerosis associated with mild to moderate tubular atrophy.

Pathogenesis of Vasculopathic

GGS

Arterial intimal fibrosis due to
Aging & HTN
Decreased Perfusion

Pathogenetically, the vasculopathic type of global glomerulosclerosis is mostly associated with chronically decreased perfusion of slow onset resulting from arterial intimal fibrosis from aging or hypertension or some vascular disease. Importantly, it has also been suggested that global glomerulosclerosis may also result from normal wear and tear phenomenon operative in the kidney as in other organs of the human body and may not reflect renal disease. In addition, global glomerulosclerosis, irrespective of the type, is almost always associated with tubular atrophy and interstitial fibrosis. This differentiates it from the involuted micglomeruli. Kriz et al. have proposed that misdirected filtration is responsible for the periglomerular and interstitial fibrosis in cases of global glomerulosclerosis, which is not observed in involuted glomeruli. This type of glomerulosclerosis is seen in renal biopsies from older patients on top of other types of glomerulopathy (reflecting age-associated glomerulosclerosis) and in hypertensive kidney disease (nephrosclerosis). Recently, it has been claimed that there are differences in the immunohistochemical staining patterns of resident glomerular cells and the fibrous components among the three types of global glomerulosclerosis; involutional, glomerulopathic and vasculopathic. On its own, vasculopathic global glomerulosclerosis has no diagnostic value in the elucidation of focal segmental glomerulosclerosis (FSGS).

TAKE HOME POINTS

- Global glomerulosclerosis arises by two principal mechanisms and hence is of two types.
- It is important to differentiate between the two types of glomerulosclerosis, i.e., glomerulopathic and vasculopathic types, as these have differing diagnostic implications.
- The two types of global glomerulosclerosis may co-exist in the same biopsy and reflect multiple forms of renal injury.
- The lesions of global glomerulosclerosis, in themselves, are non-specific and may occur in a variety of renal diseases and are not very helpful in the diagnosis of FSGS.

**Focal/global glomerular lesions-V
Case 7.**

Following are representative images from a renal biopsy done on a 4-year-old male with frequently relapsing nephrotic syndrome since past two years.

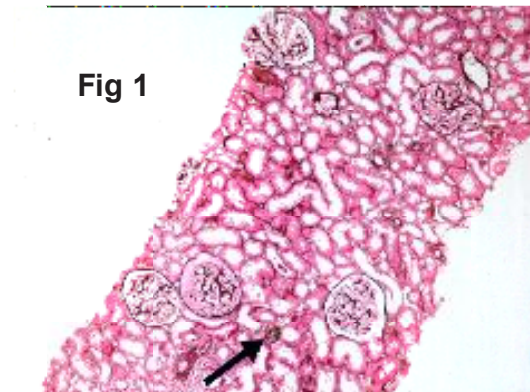


Figure 1 (Jones methanamine silver, $\times 100$) shows a low-power view of one representative area of renal biopsy from the above child. There are many glomeruli showing minor changes on light microscopy (LM). In addition, one dark staining nodule like structure is seen un-accompanied by interstitial inflammation or fibrosis (arrow). This represents an involuted glomerulus. Note the size of this glomerulus as compared with the normal glomeruli in the field. A few scattered intralobular arterioles are seen scattered throughout the field. No significant tubular atrophy is observed.

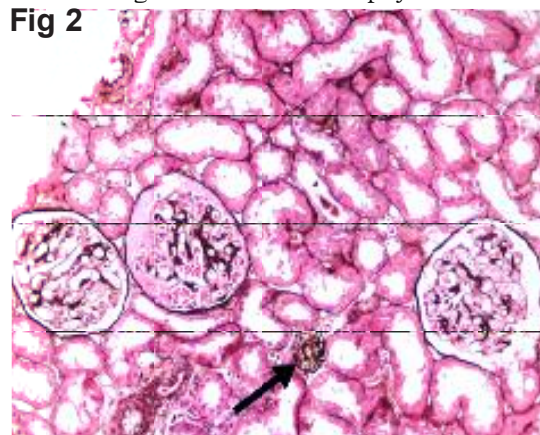


Figure 2 (Jones methanamine silver, $\times 200$) shows medium-power view of the involuted glomerulus (arrow) shown in Figure 1. Note the markedly small size and the darkly staining character of the glomerulus. There is no periglomerular fibrosis, tubular atrophy or interstitial inflammation and fibrosis. Three relatively normally appearing glomeruli are also seen in the field.

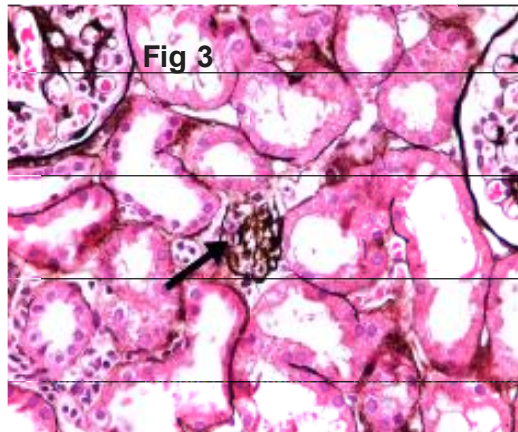


Figure 3 (Jones methanamine silver, ×400) shows high-power view of the glomerulus highlighted in Figures 1 and 2. Note that it is composed of entangled mass of black staining mesangial matrix and glomerular basement membrane giving a darkly staining nodule like appearance and a number of cells, identified by their nuclei (arrow). These cells comprise of parietal and visceral epithelial cells. There is conspicuous absence of tubulointerstitial changes in the immediate vicinity of the glomerulus.

DISCUSSION

The type of global glomerulosclerosis shown in this case and the biopsy pictures represents a distinct type of glomerulosclerosis typically identified in biopsies from children with frequently relapsing minimal change nephrotic syndrome. Although descriptions of this type of glomerulosclerosis are found in old literature, noted as “microglomeruli”, in biopsies from children with congenital or childhood nephrotic syndrome, the exact characterization and biological significance of this type of glomerulosclerosis were not clear. More recently, a number of investigators have tried to study this type of glomerulosclerosis in more detail and have proposed the name of glomerular involution for this glomerular lesion.

Traditionally, two forms of global glomerulosclerosis were widely recognized and reported in renal biopsies: the vascular (obsolescent) type and the glomerulopathic (solidified) type. These were discussed in the preceding cases in this biopsy teaching series. In this case, we discuss another type of glomerulosclerosis, which is distinct from both above types of global glomerulosclerosis and has only recently been characterized in detail. However, its description can be found in the old literature, where the term of “microglomeruli” was used for these glomeruli. In biopsies from children with recurrent nephrotic syndrome owing to minimal change nephropathy (MCN), some investigators noted small, globally sclerosed glomeruli that appeared to be distinct from global glomerulosclerosis. These small sclerosed glomeruli are best described as involuted glomeruli. The involuted glomeruli can be differentiated from the other types of global glomerulosclerosis. Most notable is the presence of viable podocytes and parietal epithelial cells, which have retained their staining characteristics, in between the matrix, and the absence of periglomerular and tubulointerstitial fibrosis.

On low power examination and silver staining, they appear as small black nodules without accompanying interstitial changes. Hence, they can easily be missed if present in low numbers. On high power, they appear as a mass of tangled network composed of remnants of glomerular basement membrane (GBM), mesangial matrix and Bowman's capsule along with entrapped viable cells. Dijkmen et al. (Dijkmen et al. *Kidney Int* 2007;71:44-52) recently studied glomerular involution in detail in children with frequently relapsing minimal change nephrotic syndrome and characterized the morphological changes in the matrix and cells observed under light microscopy (LM), immunohistochemistry (IHC) and electron microscopy (EM). They observed involuted glomeruli in 12 out of 18 biopsies from nephrotic children with MCN; the median percentage of involuted glomeruli was 6% (range 0 – 33%). They also studied a number of clinical factors and correlated

them with the number of involuted glomeruli. They found that the percentage of involuted glomeruli correlated with age at renal biopsy and the interval between onset of disease and time of renal biopsy, but not with gender, age at onset of disease, or steroid dose. Multivariate analysis showed that the interval between onset of disease and time of renal biopsy (i.e., duration of disease) was the only independent predictor. They concluded that glomerular involution is a special form of global glomerulosclerosis.

The absence of periglomerular and tubulo-interstitial fibrosis suggests a different pathogenesis from that of the classical forms of global glomerulosclerosis. It is a slow process and the clinical data suggest that involution is related to the duration of the disease process. However, the pathogenesis and the clinical significance of glomerular involution is still not clear. More studies are needed to further elucidate the pathogenesis and clinical significance of this type of glomerulosclerosis. It is important to identify this form of global glomerulosclerosis as distinct from the global glomerulosclerosis of the glomerulopathic and vasculopathic types and should be reported.

TAKE HOME POINTS

- Involuted glomeruli represent a distinct form of global glomerulosclerosis with unclear pathogenesis and still unknown clinical significance.
- The morphological changes of glomerular involution have been characterized in detail only recently. These glomeruli are characterized by a marked reduction in size (approximately one-fourth the size of an open normal glomerulus) and a distinct lack of accompanying tubular atrophy and interstitial fibrosis.
- Involuted glomeruli are typically observed in children with frequently relapsing minimal change nephrotic syndrome and their presence and relative numbers should be noted in the biopsy report.