

Renal biopsy teaching series

Focal/segmental glomerular lesions-I

By

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Case 2.

Here is a representative image from a renal biopsy done on a 15-year-old male with steroid resistant nephrotic syndrome (SRNS) associated with microscopic haematuria and hypertension. No systemic diseases. No family history of renal disease. Relevant viral serology was negative.

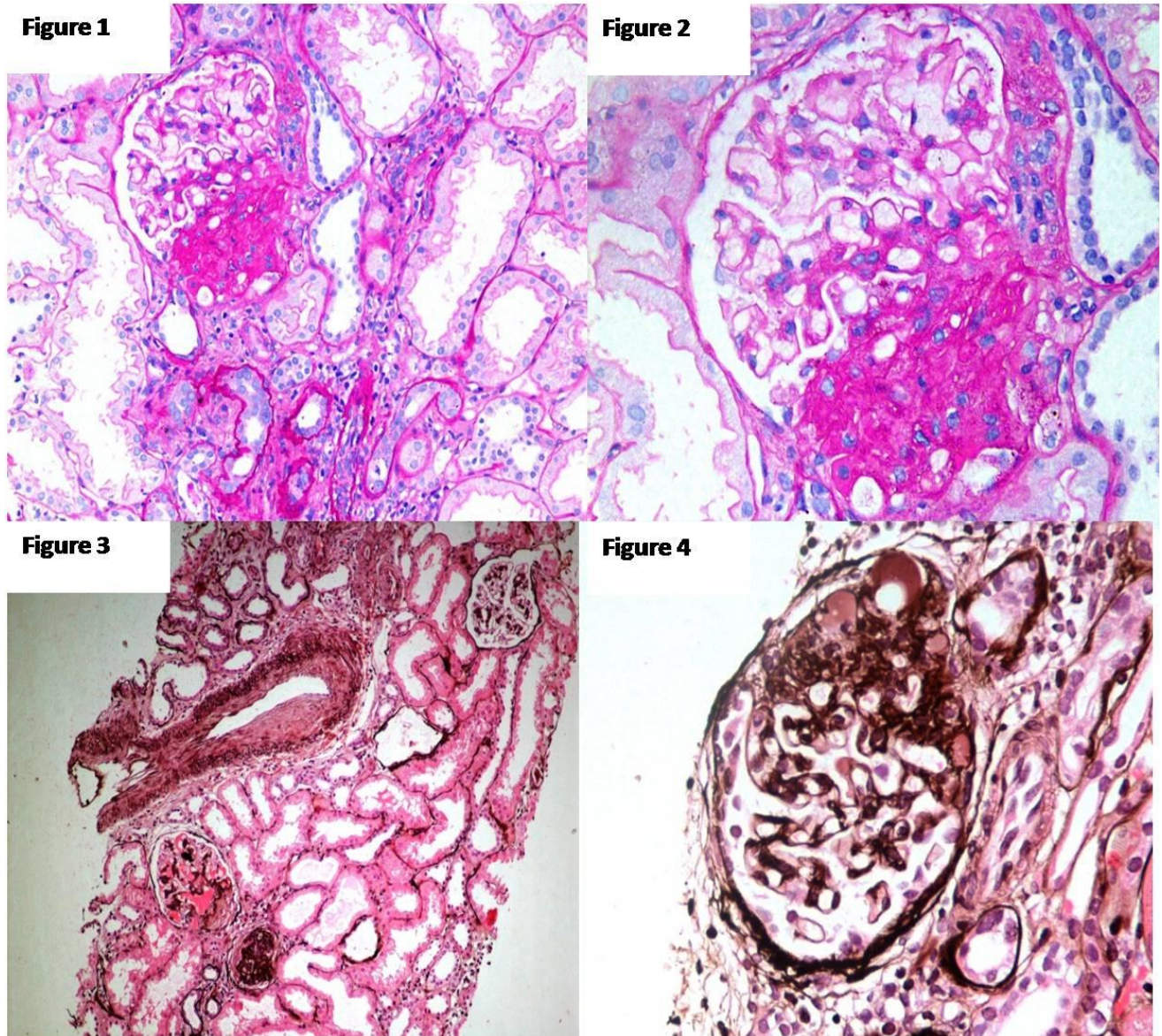
Figure 1 (Periodic acid-Schiff, $\times 200$) shows a low-power view of one representative area of renal biopsy from the above patient with one glomerulus which is showing a segmental lesion. There is a patch of tubular atrophy in the lower part of the picture associated with interstitial fibrosis and 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, $\times 400$) shows high-power view of the same glomerulus as in Figure 1 with segmental pathology. The nature of the pathology is more obvious at this magnification. It consists of segmental sclerosis and hyalinosis (in the lower one third of the glomerulus just beside the hilum of the glomerulus) and adhesion formation with Bowman's capsule. The most striking change in sclerosis consists of loss of capillary lumina; as a result of which, the affected glomerular tuft assumes a solid appearance. There is no obvious podocytopathy in this case. Figure 3 (Jones methenamine silver, $\times 100$) shows low-power view of the one representative area of the biopsy depicting a large interlobar size artery showing mild fibrointimal thickening, two relatively normal looking glomeruli, one globally sclerosed glomerulus, and mild patchy tubular atrophy. Although none of the features in this field is diagnostic of focal segmental glomerulosclerosis (FSGS), a presence of these findings should alert the pathologist to a careful search for the pathognomonic lesions of FSGS in other areas of the biopsy. Figure 4 (Jones methenamine silver, $\times 400$) shows high-power view of a similar glomerulus as shown in Figure 2, but the stain is different. The nature of the pathology is more obvious with this stain, especially the distinction between hyalinosis and sclerosis. Note that sclerotic areas stain black with silver stain whereas hyaline deposits do not stain black with this stain. The lesion is juxta-hilar in location, the common site for the origin of segmental scarring. The lower half of the glomerulus appears unremarkable, a prerequisite for the diagnosis of this category of glomerular lesions. 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 alert one to the possibility of finding of characteristic lesions of segmental scars on serial sections.

Discussion

The clinical presentation of this case is broadly similar to that of case 1 discussed in previous issue of this journal, i.e., with idiopathic nephrotic syndrome (NS), but there are some additional features not found in the previous case. The disease process is non-responsive to standard therapy with steroids commonly used in children. The response to steroids is sometimes used to classify idiopathic NS in children. Moreover, the child is of adolescent age group and has microscopic haematuria and hypertension. Although, these features may be seen in some cases of minimal change disease (MCD), but chances of the later diagnosis become less and less with the additional features of NS.

Regarding morphology of the disease, focal segmental glomerular lesions are characterized on two premises: the distribution of the lesions and the nature of the lesions. According to distribution, the lesions show focal (affecting less than 50% of glomeruli) and segmental (affecting only part of the involved glomerulus) involvement on light microscopic (LM) level. According to the nature of the lesion, it 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.



The characteristic lesion of FSGS consists of segmental sclerosis and hyalinosis involving one or more tufts in the involved glomeruli. Sclerosis is most easily identified by the solid looking appearance of the affected tuft (in contrast to the normal sieve-like appearance of glomerular tufts) on LM. 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 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. Other components of the renal parenchyma, besides glomeruli, also show pathological changes. These consist of various forms of arteriosclerosis, tubular atrophy and interstitial inflammation. Sometimes, changes may be found in the vascular and tubulointerstitial compartments and the sampled glomeruli in the biopsy on initial sections may not show characteristic segmental scars. In such cases, ordering more serial sections, and in some cases, sectioning the whole renal biopsy material may prove fruitful in finding the segmental lesion. Among all the glomerular pathological lesions, this is the one which poses significant challenges to the nephropathologists and nephrologists in diagnosis and management.

FSGS is a morphological pattern of glomerular response to a variety of injuries and not a specific disease. Several specific glomerular diseases (eg. IgA nephropathy) and secondary diseases can produce this morphological pattern. Morphologic spectrum of the lesion is broad and not all variants of FSGS exhibit sclerosis or hyalinosis. Clinical presentation of FSGS is also non-specific, especially in adults. The main presenting feature is NS, but it can present with non-nephrotic proteinuria, microscopic or macroscopic haematuria or chronic renal insufficiency (in advanced cases). Hence, an accurate diagnosis and classification requires a correlation of clinical, laboratory, serological and pathological findings including LM, immunofluorescence and electron microscopy.

Take home points

- In focal/segmental lesions, the distribution of pathological lesions is non-uniform on light microscopy (LM), in that less than 50% of glomeruli are affected (focal) and only portions (segments) of the involved glomeruli (segmental) are affected. Remaining glomeruli show minor changes under LM.
- The pathology may or may not be diffuse and global on immunofluorescence (IF) and electron microscopy (EM).
- The LM changes of FSGS are not specific and they can present in a variety of ways.
- This category is heterogeneous and entails a broad differential diagnosis.
- An accurate diagnosis and classification requires a correlation of clinical, laboratory, serological and pathological findings including LM, IF and EM.