Pathology of minimal change nephropathy and segmental sclerosing glomerular disorders

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Abstract

Minimal change nephropathy is relatively uncontroversial. This can be defined as the condition associated with the nephrotic syndrome in which glomeruli have no abnormality on light microscopy. Segmental sclerosing glomerular disorders are often called focal segmental glomerulosclerosis, one of the most controversial terms in kidney disease. The tubular opening is the earliest site at which segmental changes appear. These tip changes are not a disease in themselves. The glomerular tip lesion has tip changes in otherwise normal glomeruli. Tip changes in large glomeruli with mesangial increase can be called early classical segmental sclerosing disease. This can progress to give abnormalities at various sites, or late classical segmental sclerosing disease, corresponding with the classical descriptions of focal segmental glomerulosclerosis. Hilar abnormalities are a characteristic finding in reduced glomerular numbers. Focal segmental glomerulosclerosis is an ambiguous term, applied to many different types of segmental sclerosing glomerular disorders.

Keywords: FSGS; minimal change nephropathy; nephrotic syndrome; pathology

Introduction

Although minimal change nephropathy is a difficult diagnosis to make, the disorder is well defined and relatively uncontroversial. Segmental sclerosing glomerular disorders are often grouped and called focal segmental glomerulosclerosis. This term is in widespread use but is one of the most controversial subjects in kidney disease. Minimal change nephropathy and so-called focal segmental glomerulosclerosis are often studied together for the traditional reason that they seemed to be the findings in lipoid nephrosis in the days when that diagnosis was used and considered a single type of disease.

Minimal change nephropathy

Definition of minimal change nephropathy and its prevalence

This can be defined as the condition associated with the nephrotic syndrome in which glomeruli have no significant abnormality on light microscopy. One problem is that the name is misapplied when the clinical features do not include the nephrotic syndrome. Another problem is that there are no objective standards to allow the pathologist to determine whether there are significant abnormalities. Even so, when used correctly the diagnosis is of great help to nephrologists in management.

Most children with nephrotic syndrome do not have a renal biopsy and are assumed to have this condition, which is still the commonest finding in those who have a biopsy. The condition is the third commonest finding in adults with the nephrotic syndrome after membranous nephropathy and segmental sclerosing glomerular disorders. Only a few people with minimal change nephropathy have an apparent cause, either a drug such as a non-steroidal anti-inflammatory analgesic or a neoplasm such as Hodgkin’s lymphoma, although the pathologist cannot identify these causes from a renal biopsy specimen.

Diagnosis of minimal change nephropathy

A renal biopsy specimen in minimal change nephropathy shows the amount of tubular atrophy expected for the age of the person biopsied. Glomeruli appear of normal size and cellularity, and have no segmental abnormalities (Figure 1) [1,2]. The main differential diagnoses are early membranous nephropathy and a
Segmental sclerosing glomerular disorder. Membranous nephropathy is easily excluded by satisfactory immunohistological study, which shows regular granular deposition of IgG and complement on the outside of all glomerular capillary loops in membranous nephropathy, but either no deposition of immunoproteins or a little mesangial deposition of IgM in minimal change nephropathy. In the nephrotic syndrome the first site within glomeruli that segmental changes appear is next to the tubular opening, and this area should always be examined to exclude a segmental disorder. Only one abnormality has to be found in one glomerulus to rule out minimal change nephropathy. A small specimen may not allow the pathologist to see many glomeruli and may not allow confident exclusion of a segmental sclerosing disorder, especially in children, in whom segmental disorders may not affect every glomerulus and may be only in deep cortical glomeruli. In practice electron microscopy is no help in the diagnosis of minimal change nephropathy.

Two tubular features in minimal change nephropathy
The nephrotic syndrome causes hypercoagulability and one effect of this is renal vein thrombosis. The only sign of this in a renal biopsy specimen may be acute tubular damage, but this can also be an effect of other things such as fluid depletion. Sometimes minimal change nephropathy is treated with ciclosporin and this may cause ischaemia of the kidney that produces tubular atrophy out of proportion to the person’s age.

Segmental sclerosing glomerular disorders

Definition of focal and segmental
These terms are widely misused. A focal glomerular abnormality is one that affects only some glomeruli, not all, when the condition is called diffuse. A segmental glomerular abnormality is one that affects only part of the glomerular tuft, not all, when the condition is called global. A focal disorder is not necessarily segmental, and a segmental disorder is not necessarily focal, although the terms focal and segmental are often automatically linked.

Definition of focal segmental glomerulosclerosis
This cannot be defined in a sensible, useful, unambiguous way [3,4]. This is because the term is applied with two vague meanings. One is the clinical usage, which developed from the days of lipoid nephrosis, of a condition associated with the nephrotic syndrome in which there are segmental sclerosing changes in glomeruli. The other is the pathological usage, which has expanded with time as there was realization that segmental sclerosing changes can be seen in glomeruli in many different conditions, not necessarily associated with the nephrotic syndrome. Many texts discuss focal segmental glomerulosclerosis without recognition of this ambiguity but with the statement that all conditions with segmental sclerosing abnormalities look the same. This makes several difficulties. One is that any attempt to investigate segmental sclerosing disorders is dismissed as just another study of focal segmental glomerulosclerosis or a variant of it. Another is that no-one can be sure that any study of so-called focal segmental glomerulosclerosis, either clinical or pathological, is considering the same condition as any other study. Little progress will be made in understanding segmental sclerosing glomerular disorders unless the term focal segmental glomerulosclerosis is used with more discrimination.

Types of segmental sclerosing glomerular abnormalities
Segmental sclerosing disorders do not all look the same. For instance, the late, healed stages of vasculitic glomerulonephritis are easily diagnosed because they have a well-defined outline, obliterate part of the glomerular tuft and the overlying Bowman’s space and can be at any site within glomeruli [5,6]. Nodules in diabetic glomerulopathy are distinctive and are distributed around the periphery of glomeruli [7].

Careful study of other segmental abnormalities allows the pathologist to identify several different types [3,4]. Attention should be paid to the position of segmental changes within glomeruli, the structure of those changes, the proportion of glomeruli affected, the size of glomeruli and the state of glomeruli away from segmental changes. The tubular opening is the earliest site at which segmental changes appear in the nephrotic syndrome [8,9]. This is because such changes are a consequence of prolapse of an acutely swollen glomerular tuft into the tubular opening that damages epithelial cells of the glomerulus (Figure 3). This causes accumulation of foamy macrophages at this site and adhesion of the tuft to Bowman’s capsule (Figure 4).
Later there may be only a thin adhesion at this site or there may be various amounts of hyaline and sclerosed material [10,11]. Any non-vasculitic segmental changes away from the tubular opening are late and any changes with hyaline material or sclerosed material are late [8,9,12]. This is not often appreciated. Segmental sclerosing changes at any site in the tuft may be caused by direct damage to glomerular visceral epithelial cells [8]. Some descriptions of focal segmental glomerulosclerosis say that segmental changes in this condition are typically at the glomerular hilum. Such changes are late. Hilar sclerosing abnormalities are a characteristic finding among other consequences of reduced glomerular numbers, also called reduced renal mass or states of glomerular hyperperfusion or overload, although they are not restricted to such states (Figure 5) [6,8,9,13–15]. Another characteristic finding in reduced glomerular numbers is that surviving glomeruli are large [9,13].

Use of serial sections allows the pathologist to determine the position of changes within glomeruli and also the proportion of glomeruli affected. Some segmental changes are genuinely focal but some are
found in every glomerulus and should be called diffuse. This is not apparent on a few random sections [9,16].

Disorders with segmental sclerosing abnormalities

Because segmental sclerosing changes are complications of various events in glomeruli, they can occur in many different diseases. If the underlying disease is recognized by the pathologist, this should be given as the diagnosis, rather than as the combination of that disease with focal segmental glomerulosclerosis. For example, the segmental abnormalities that develop next to the tubular opening and can be called tip changes and are complications of prolapse of the tuft, and are not a disease in themselves. Tip changes are common, although they are not often looked for or appreciated, in many conditions, including membranous nephropathy, diabetic glomerulopathy, lupus nephritis, acute post-infective glomerulonephritis, renal allograft rejection and haemolytic uraemic syndrome not due to verocytotoxin (Figures 4 and 6) [11,17,18]. Late stages of many conditions such as IgA nephropathy and those mentioned are complicated by the development of segmental sclerosing changes, that can be due to various combinations of tip changes, overload effects, epithelial damage, vasculitic disorders and other mechanisms not yet discovered (Figure 7).

In the nephrotic syndrome there may be segmental abnormalities without a diagnosable underlying condition such as membranous nephropathy. The pathologist should determine two things, the position of the segmental abnormalities and the state of the rest of the glomerulus. If the abnormalities are at various sites in the tuft, whether at multiple sites within a glomerulus or at different sites in different glomeruli, the condition can be regarded as the one most closely corresponding with the classical, textbook, clinical form of focal segmental glomerulosclerosis (Figure 8). This is likely to be difficult to treat, is likely to progress to renal failure and has a chance of recurrence in a renal allograft. This is sometimes called malignant focal segmental glomerulosclerosis if the clinical course is especially rapid.

What should be realized is that this is already a late condition at diagnosis, shown by the facts that the segmental changes are not only at the tubular opening and are hyalinized and sclerosed, and that there is extensive tubular atrophy. A name that can be used is late classical segmental sclerosing disease [3,4,9]. The

Fig. 6. Glomerulus in membranous nephropathy. There is a tip change.

Fig. 7. Glomerulus in late lupus nephritis with multiple areas of sclerosis and capsular adhesion.

Fig. 8. Cortex in late classical segmental sclerosing disease with tubular atrophy and multiple areas of sclerosis in glomeruli.
early form of this is easily missed and misunderstood. This takes the form of tip changes in glomeruli that are large and have mesangial increase to different extents, and can be called early classical segmental sclerosing disease (Figure 9) [3,4,9]. This may have been called mesangial proliferative glomerulonephritis or even minimal change disease by others. This is not the same as the glomerular tip lesion, which is the condition found in the nephrotic syndrome in which there are tip changes in glomeruli that otherwise look normal, and would have been called minimal change nephropathy if there were no segmental abnormalities (Figure 10) [3,4,9,12,16,19]. The name glomerular tip lesion has been misapplied by others to the early form of classical segmental sclerosing disease (Figure 9) and even to the tip changes that can be seen in many conditions (Figures 4 and 6). The glomerular tip lesion is unlikely to be found in a series of so-called focal segmental glomerulosclerosis and is much more likely to be found in a series of minimal change nephropathy [20].

Most renal biopsy specimens with segmental sclerosing abnormalities but without an identifiable underlying disease are not from people with the nephrotic syndrome. These are from people with various amounts of proteinuria, renal impairment and hypertension, and are found to have segmental abnormalities that are late, can be at any site in the tuft, and are genuinely focal, that is they are not in every glomerulus (Figure 11). This condition can be called genuinely or truly focal segmental sclerosing disease [3,4,9]. In the nephrotic syndrome segmental abnormalities are generally in all or most glomeruli [3,4,9,16].

Another condition often considered with segmental sclerosing disorders

Texts on focal segmental glomerulosclerosis often include a section on the condition called collapsing glomerulopathy, that is a typical glomerular finding associated with infection with human immunodeficiency virus, although it may occur without such infection. In this condition there is collapse of the mesangium and prominence of glomerular epithelial cells (Figure 12). This is almost always a diffuse and global disorder rather than focal and segmental [1,2].
Minimal change nephropathy is an excellent diagnosis if used with care and applied properly. Focal segmental glomerulosclerosis is such an ambiguous term that if it is used at all it should be qualified to indicate whether it is applied to various segmental sclerosing abnormalities associated with the nephrotic syndrome or with other states such as reduced renal mass or with recognizable disorders such as membranous nephropathy.

References

Fig. 12. Cortex in collapsing glomerulopathy. The whole of each glomerulus is abnormal.