Collagen Type III Glomerulopathies

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The 2 rare disorders characterized by the pathological accumulation of collagen type III in glomeruli are discussed. These are collagenofibrotic glomerulopathy, also known as collagen type III glomerulopathy, and the nail-patella syndrome. Although there are similarities in abnormal morphology, with type III collagen in mesangium and/or capillary walls, there is no genetic or pathogenic link to them. Collagenofibrotic glomerulopathy presents either in childhood, often with a family history suggesting autosomal recessive inheritance, or in adults as a sporadic occurrence. Proteinuria is the typical manifestation, with progression to ESRD in approximately 10 years. Although there is markedly elevated serum precursor collagen type III protein in the circulation, the usual manner of diagnosis is with kidney biopsy, which discloses type III collagen in subendothelial aspects of capillary walls and often in the mesangial matrix. Glomerular involvement in the nail-patella syndrome invariably presents in a patient with an established diagnosis of this multisystem disorder with orthopedic and cutaneous manifestations. It is owing to mutations in the gene LMX1B. Although the lesion may be asymptomatic, it is usually manifested by proteinuria. Structural lesions are of collagen type III within glomerular basement membranes, different in distribution to collagenofibrotic glomerulopathy. The clinical course is variable.

Key Words: Nail-patella syndrome, Collagen type III, Collagenofibrotic glomerulopathy, Renal electron microscopy, Glomerular fibrosis

Glomerular extracellular matrix is composed of capillary basement membranes and mesangial matrix. These have similar, but not identical, compositions. Mesangial matrix is composed of a variety of substances including fibronectin, laminin, collagen type IV (with minor type V), and sulfated glycosaminoglycans. The major constituent of basement membranes is type IV collagen, with a minor component of type V collagen, as well as laminin, entactin, and sulfated proteoglycans.[1]

Diseases of glomeruli, either initially or as a consequence of chronic damage, may be characterized by increased extracellular matrix, especially type collagen IV. Most notable is diabetic nephropathy, with basement membrane and mesangial matrix greatly increased.[2] There are several disorders whose morphological abnormalities are the result of the accumulation of collagens not intrinsic to glomerular extracellular matrix. Two of the more interesting of these disorders are considered in this review. In the kidney, type III collagen normally is found in the interstitium and blood vessel walls. Collagen type III fibrils are long and straight, closely approximated, and in parallel array, with periodicity of approximately 60 nm. In the disorders discussed herein, the fibrils are most often curved and frayed at the ends. They are also loosely aggregated. They are typically genetically determined and may be a component of a systemic disorder.

Collagenofibrotic Glomerulopathy

Collagenofibrotic glomerulopathy was initially described as a possible new disease by Arakawa and colleagues at the annual meeting of the Japanese Society of Nephrology in 1979, in a patient with renal functional impairment and unusual renal biopsy findings.[3] Electron microscopic evaluation of the glomeruli disclosed banded collagen fibrils in the mesangium and capillary walls. These investigators ultimately termed the lesion collagenofibrotic glomerulopathy. It has since been documented predominantly in Japan,[4-7] although at this time, reports from Europe, South America, North America, and other countries in Asia indicate that this is an uncommon disorder with worldwide presence.[8-14]

Although type III collagen is widely distributed as a component of the extracellular matrix, it is not found in normal glomeruli; however, it is a component of many diverse glomerular lesions as they undergo fibrosis.[4] These include organizing crescents, fibrosis surrounding the afferent arteriole as it enters the tufts, especially in older individuals, the urinary spaces of ischemic glomeruli, and occasionally in mesangial matrix in segmental glomerulosclerosis and diabetic glomerulosclerosis.[15]

Type III collagen is a homotrimer of 3 identical alpha-1 chains encoded by a single gene (COL3A1) on chromosome 2 located at q24.3-q31. It is initially synthesized as a large precursor molecule known as type III procollagen; following cleavage of its N-terminal peptide, it is converted into type III collagen. Consequently, serum levels of procollagen type III peptide (PIIINP) are elevated in patients with many diseases characterized by fibrosis. Increased serum and urinary levels of PIIINP are indicators of renal fibrosis; however, they may be increased in patients with renal failure, often twice normal levels regardless of the form of renal disease. On the other hand, levels ranging from 10 to 100 times normal are detected in patients with collagenofibrotic glomerulopathy.[16,17]

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Collagenofibrotic glomerulopathy, also known as collagen type III glomerulopathy (these terms will be used interchangeably in this review), is characterized by the accumulation of massive amounts of collagen type III in glomerular capillary walls, largely in subendothelial locations, and in mesangial matrix. Although the light microscopic features, to be discussed later in the text, are striking and are very suggestive of this disorder, the ultrastructural abnormalities are the diagnostic aspects.

This disorder may become apparent at any age, although most reported patients are adults; there is no gender predilection. It commonly presents with proteinuria that, in more than 50% of the patients, is in the nephrotic range. Hematuria, when detected, is microscopic. Hypertension occurs early, and approximately 60% of the patients have high blood pressure at presentation. Renal function is usually normal or slightly reduced at presentation. However, progressive decline in creatinine clearance occurs in some adult and pediatric patients, culminating in ESRD in approximately 50%.[9,18,19] Anemia of chronic disease is regularly detected well before the development of advanced renal failure.[15] Three of the 10 pediatric patients described by Gubler and colleagues[8] also had a thrombotic microangiopathy; it is of note that 2 additional patients were reported to have an inherited factor H deficiency.[20,21] Evaluation of one patient with inherited factor H deficiency, persistent hypocomplementia, and collagen type III glomerulopathy suggested that factor H deficiency-associated glomerular damage, as documented by 3 renal biopsies, evolved to collagen type (III) accumulation (glomerulopathy), thereby possibly explaining the potential link between these disorders.[20] Nevertheless, the relation of these abnormalities to collagenofibrotic glomerulopathy is uncertain.

CLINICAL SUMMARY

- Accumulation of collagen type III in glomeruli is a feature of 2 different and likely unrelated, rare, usually inherited diseases (collagenofibrotic glomerulopathy and the nail-patella syndrome) requiring electron microscopy of renal biopsies for diagnosis. This emphasizes the need for comprehensive pathological evaluation.
- The genetic basis of the nail-patella syndrome is known (a mutation in gene LMX1B), although similar information is not available for collagenofibrotic glomerulopathy.
- Collagenofibrotic glomerulopathy may present at almost any age.
- Effective therapy for either is not available.

In most reported patients, the manifestations were of a sporadic nature, without involvement of other family members. However, several reports describe other affected family members, suggesting autosomal recessive inheritance,[8,19] especially in children. Thus, it is likely that there are 2 forms of the disease based on age of presentation. The series by Gubler describes some patients with this lesion complicated by thrombotic microangiopathy, and some siblings with the hemolytic uremic syndrome without collagenofibrotic glomerulopathy.[8]

Laboratory evaluation for collagenofibrotic glomerulopathy reveals nonspecific features of glomerular disease except for a greatly elevated PIIINP; typically, however, this test is not considered in the routine prebiopsy series of diagnostic studies. Thus, unless there is a very high index of suspicion, collagenofibrotic glomerulopathy is not diagnosed unless or until a biopsy is performed.[15]

Pathological Features

The characteristic abnormalities of considerable accumulation of type III collagen are easily appreciated by light microscopy, with the usual stains performed on renal biopsies, although immunostain for type III collagen and/or electron microscopy is necessary to characterize specifically the abnormalities.

By light microscopy, the glomeruli are enlarged with lobular architecture, widened mesangial regions, and thick capillary walls. This is the result of accumulation of homogeneous material in subendothelial aspects of most capillary walls and in the mesangium; there is no increase in cellularity (Fig 1A). The abnormal extracellular infiltrate is negative or weakly positive with periodic acid-Schiff, negative with periodic acid-methenamine silver (Fig 1B), blue with Masson trichrome, and negative with Congo red. Basement membranes have usual thickness, and capillary walls are typically single contoured, although few double contours may be present. As the disorder progresses, segments of sclerosis with insudative lesions occluding some capillaries are evident. Crescents are not a feature of this glomerulopathy. Tubular atrophy with interstitial fibrosis reflects advancing changes, and arterial intimal fibrosis and arteriolar insudative lesions (hyalinosis) are generally associated with hypertension. Immunoperoxidase stain for type III collagen indicates the abnormal extracellular infiltrate to be stained positive.[22]

Immunofluorescence is negative for immunoglobulin and complement components, except when segmental glomerulosclerosis supervenes. However, as indicated previously, fluorescein-conjugated antibodies to collagen type III are positive in mesangial regions and capillary walls (Fig 2). As collagen type III is found in many glomerular disorders, often at an advanced stage, primarily in the mesangium, it is clear that the mere identification of collagen III in glomeruli is not diagnostic. Thus, the use of an immunostain to document the presence of type III collagen should be interpreted in light of the other glomerular abnormalities, including possible chronic injury.