Clinical and Pathologic Features

Diabetic nephropathy is the most common cause of ESRD and develops in 20% to 30% of patients with diabetes. Time to develop overt diabetic nephropathy is typically 15 years in type 1 diabetes, with a less clear time course in type 2 diabetes (because its onset may not be known precisely). While patients typically develop albuminuria followed by overt proteinuria and glomerular filtration rate (GFR) loss, the degree of albuminuria is not necessarily linked to disease progression. Patients initially have hyperfiltration and increased GFRs, with progressive decline.

Light microscopy: Classic findings include mesangial expansion mainly due to increased mesangial matrix, which can be diffuse and, as kidney disease progresses, more typically nodular (Kimmelstiel-Wilson nodules). The nodules are round with a hypocellular matrix core surrounded by patent capillary loops, resembling a sunflower. Microaneurysms of glomerular capillaries are often seen along with mesangiolysis or nodules. Segmental glomerulosclerosis, especially at the tubular outlet (ie, tip lesion), is common in later stages of diabetic nephropathy. Hyalinosis may be present within the glomerular tuft under the endothelial cells or under the parietal epithelial cells (capsular drop). Hyalinosis of afferent and efferent arterioles is common and although not pathognomonic, is rare in other conditions. In type 1 diabetes, interstitial fibrosis and tubular atrophy follow glomerular lesions and may be less severe or proportional to diabetic glomerulopathy. In type 2 diabetes, in which arteriosclerosis is commonly present, the lesions are more heterogeneous, and chronic tubulointerstitial injury may be more severe than the diabetic glomerulopathy.

Immunofluorescence microscopy: Diffuse linear accentuation of glomerular and tubular basement membranes with IgG (and κ and λ light chains) and albumin is typical. Nonspecific segmental staining of hyaline deposits or glomerular sclerotic regions for IgM, C3, and C1q is common in advanced disease.

Electron microscopy: Diffuse thickening of GBMs is usually the earliest structural change. Tubular basement membranes of nonnaphroplastic tubules are also thickened. Mesangial regions are expanded, predominantly due to accumulation of mesangial matrix. There are no immune complexes. Podocytes show variable foot process effacement, especially in advanced stages.

Etiology/Pathogenesis

Hyperglycemia is the main initiator of diabetic kidney disease. Hyperlipidemia and insulin resistance are additional contributors in type 2 diabetes. Increased oxidative stress, inflammation, and aberrant growth factors are all implicated as mechanisms of injury. Accumulation of extracellular matrix in the mesangium is the key morphologic finding. The classic Kimmelstiel-Wilson nodules are postulated to be the consequence of repeated mesangiolysis, with an exuberant repair response. Podocyte and endothelial cell injuries also play important roles in the progression of the disease.

Differential Diagnosis

Nodular glomerulosclerosis can also be seen in monoclonal immunoglobulin deposition disease (MIDD), amyloidosis, idiopathic nodular glomerulosclerosis, membranoproliferative glomerulonephritis, and more rarely in fibrillary and immunotactoid glomerulopathy, fibronectin glomerulopathy, collagen type III glomerulopathy, congenital cyanotic heart disease, and cystic fibrosis. Immune complex membranoproliferative glomerulonephritis is typically associated with prominent mesangial hypercellularity. Immunofluorescence and electron microscopy studies can rule out most of these conditions. Congo Red staining should be performed when amyloidosis is suspected. Idiopathic nodular glomerulosclerosis may closely mimic diabetic nephropathy and is a diagnosis of clinical exclusion. The linear GBM staining in anti-GBM glomerulonephritis is typically much stronger than the dull and modest linear staining in diabetic nephropathy. Moreover, albumin staining is absent in anti-GBM glomerulonephritis, while diffuse in diabetic nephropathy.

Key Diagnostic Features

- Increased mesangial matrix, nodular glomerulosclerosis
- Diffuse GBM thickening by electron microscopy
- Concomitant hyalinosis of afferent and efferent arterioles
Figure 1. (A) Diabetic nephropathy with diffuse mesangial expansion and arteriolar hyalinosis (red arrow). (B) Diabetic nephropathy with nodular mesangial expansion (Kimmelstiel-Wilson nodules) and concomitant hyalinosis of afferent and efferent arterioles (red arrows; Jones silver stain).

Figure 2. Advanced diabetic nephropathy with Kimmelstiel-Wilson nodule (upper asterisk) with adjacent mesangiolysis (yellow arrow) and a microaneurysm (white arrow) with prominent arteriolar hyalinosis (red arrow). There is a capsular drop (lower asterisk) on Bowman capsule (Jones silver stain).

Figure 3. Advanced diabetic nephropathy with prominent thickening of glomerular basement membranes with expanded mesangium, predominantly due to increased mesangial matrix. There is segmental foot process effacement, indicative of podocyte injury (electron microscopy).

Figure 4. Diabetic nephropathy with tubular basement membrane thickening in nonatrophic tubules (electron microscopy).