REVIEW

Distinguishing diabetic nephropathy from other causes of glomerulosclerosis: an update

K O Alsaad, A M Herzenberg

Diabetic nephropathy is a common cause of end-stage renal disease worldwide. It is characterised by diffuse or nodular glomerulosclerosis, afferent and efferent hyaline arteriosclerosis, and tubulointerstitial fibrosis and atrophy. Diffuse and nodular diabetic glomerulosclerosis share similar histological features with other clinical conditions. Immunofluorescence and electron microscopy studies, and clinicopathological correlation are essential to differentiate diabetic nephropathy from other conditions that result in diffuse and nodular glomerulosclerosis.

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Diabetic nephropathy is a major cause of end-stage renal disease worldwide. It is clinically defined as progressively increasing proteinuria accompanied by increasing blood pressure and impairment of glomerular filtration. Histologically, diabetic nephropathy is characterised by diffuse or nodular glomerulosclerosis, tubulointerstitial fibrosis and atrophy, and variable degrees of hyaline arteriosclerosis and arterial sclerosis. Diabetic nodular glomerulosclerosis shares similar histological features with other clinical conditions that produce a nodular glomerulosclerosis injury pattern such as membranoproliferative glomerulonephritis, monoclonal immunoglobulin deposition disease, amyloidosis, fibrillar glomerulopathy and idiopathic nodular glomerulosclerosis. A detailed histopathological evaluation of renal biopsy specimens with the aid of immunofluorescence and electron microscopy studies, and clinicopathological correlation is mandatory to reliably distinguish diabetic nephropathy from other causes of nodular glomerulosclerosis. In this article, the clinical features, pathogenesis and histopathological features of diabetic nephropathy are reviewed. The morphological features of the conditions that result in diffuse and nodular glomerulosclerosis are discussed, with an emphasis on the distinguishing histological, immunofluorescence and ultrastructural features that help in making an accurate diagnosis of diabetic nephropathy.

NATURAL HISTORY AND PATHOGENESIS OF DIABETIC NEPHROPATHY

Diabetic nephropathy is the single most common cause of end-stage renal failure worldwide,¹ and a major indication for dialysis and transplantation. Approximately 40% of patients with diabetes develop diabetic nephropathy. The typical early clinical presentation of diabetic nephropathy is

microalbuminuria, which generally appears 5–15 years after the patient is diagnosed with diabetes mellitus. With time, the urinary excretion of protein increases and becomes less selective, with the eventual development of nephrotic-range proteinuria in many patients. This is usually associated with a decrease in glomerular filtration rate. Once microalbuminuria/proteinuria presents, renal function progressively declines and end-stage renal disease develops in a considerable number of patients.

The pathophysiological mechanisms that eventually lead to nephropathy and the morphological features of diabetic renal lesions are similar in type 1 and type 2 diabetes mellitus.² Various factors are involved in the pathogenesis of diabetic nephropathy including genetic susceptibility to develop nephropathy,³ and haemodynamic and biochemical changes. The glomerular haemodynamic changes include hyperfiltration and hyperperfusion, which are in part due to decreased afferent arteriolar resistance. Efferent arteriolar resistance is also decreased. These changes are mediated by the effect of various biochemical factors, including angiotensin II, nitrous oxide, atrial natriuretic factor, glucagon and insulin.⁴ Glomerular hyperfiltration and hyperperfusion may play an essential part in mesangialisation and glomerular basement membrane changes in diabetic nephropathy.⁵

Currently, it is believed that a hyperglycaemia-induced defect in the mitochondrial electron transport chain, resulting in increased production of reactive oxygen species and increased oxidative stress, is a common mediator of the pathophysiological effects of hyperglycaemia and subsequent diabetic nephropathy⁶ (fig 1). The increased oxidative stress activates glycation and formation of advanced glycation end products, and formation of cytokines and growth factors. An increased flux of glucose through the hexosamine pathway leads to increased formation of transforming growth factor β .⁷ Hypertrophic and fibrogenic transforming growth factor β plays an important part in the development of glomerulosclerosis and tubulointerstitial fibrosis by stimulating the production of extracellular matrix protein collagen types I, III and IV and fibronectin, and inhibits the degeneration of extracellular matrix components through inhibition of matrix metalloproteinases.⁸ Increased angiotensin II plays an important part in the pathogenesis of diabetic nephropathy; it causes a

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Abbreviations: GBM, glomerular basement membrane; ING, idiopathic nodular glomerulosclerosis; MIDD, monoclonal immunoglobulin deposition disease; PAS, periodic acid Schiff; TBM, tubular basement membrane

Figure 1 Simplified schematic representation of the pathogenesis of diabetic nephropathy.

preferential constriction of the efferent glomerular arteriole, increases glomerular capillary permeability to protein, stimulates advanced glycation end product formation, and stimulates mesangial cell proliferation and accumulation of mesangial matrix by inducing many proinflammatory and fibrogenic cytokines, chemokines and growth factors.⁹

HISTOPATHOLOGICAL FEATURES OF DIABETIC NEPHROPATHY

Light microscopic features

Structural abnormalities of diabetic nephropathy are similar in type 1 and type 2 diabetes,² and all renal compartments (glomeruli, tubulointerstitium and renal vasculature) can be affected. The earliest morphological change in diabetic nephropathy is mesangial expansion (fig 2A) due to increased mesangial matrix deposition and a mild increase in mesangial cellularity, and hypertrophy of mesangial cells.¹⁰ The characteristic histological changes of diabetic nephropathy are diffuse and nodular glomerulosclerosis, and afferent and efferent hyaline arteriosclerosis. In diffuse diabetic glomerulosclerosis, there is diffuse thickening of the glomerular basement membrane (GBM; fig 2B), which early in the disease process cannot be appreciated by light microscopy. As the disease progresses, the mesangial matrix continues to accumulate, along with mesangial cells. This results in a characteristic nodular glomerulosclerosis pattern (Kimmelstiel–Wilson nodules; fig 2C). These sclerotic, acellular nodules can be segmental and localised, or globally involving the glomerular tufts. The degree of nodular accentuation tends to increase with the clinical duration of diabetes (fig 2D). The sclerotic nodules are usually peripherally located, have a lamellated appearance on silver stain (fig 2E), and are generally positive for periodic acid Schiff (PAS) stain. Red blood cell fragments may be present in the sclerotic nodules. Areas of mesangiolysis with foam cells and loss of matrix and attachments of mesangium to the peripheral capillary loop are often present. This results in glomerular capillary microaneurysms, usually found surrounding the expanded Kimmelstiel–Wilson nodules. Insudation and accumulation of plasma proteins result in hyalinosis between the glomerular endothelium and the GBM (fibrin cap; fig 2F), and between the glomerular tuft and Bowman's capsule (capsular drop). Kimmelstiel–Wilson nodules, fibrin caps and capsular drops are all specific but not pathognomonic to diabetic nephropathy.

Afferent and efferent hyaline arteriosclerosis is a frequent histological finding and the efferent arteriolar hyalinisation is specific for diabetic nephropathy (fig 2G). As progressive

hypertensive nephropathy can cause some glomerular structural changes similar to diffuse diabetic nephropathy, efferent arteriolar hyalinisation is an important morphological feature distinguishing diabetic nephropathy from hypertensive nephropathy, which affects the afferent but not the efferent arteriole.

Patients with diabetic nephropathy are at increased risk of developing cardiovascular disease,^{11,12} particularly patients with marked proteinuria. Patients with increased cardiovascular morbidity often show hypertensive intrarenal arteriosclerosis of variable severity. This includes atherosclerotic changes of the intima, splitting of the internal elastic lamina, medial hypertrophy and partial replacement of the muscular coat with fibrous tissue. Secondary segmental glomerulosclerosis can occur and is a common cause of nephrotic syndrome in patients with diabetes.

Interstitial fibrosis and tubular atrophy occur in proportion to the severity of glomerulosclerosis. A variable degree of interstitial mononuclear inflammatory cell infiltrate is often present in areas of interstitial scarring. Acute pyelonephritis and papillary necrosis can complicate diabetic nephropathy.

Immunofluorescence microscopy features

A mild to moderate linear staining of the GBM and tubular basement membranes (TBMs) for immunoglobulin (Ig) G and albumin is generally present in diabetic nephropathy (fig 3). Occasionally, non-specific staining of IgM and C3 is present in sclerotic nodules. Although anti-GBM-mediated glomerulonephritis is readily distinguished from diabetic nephropathy by light microscopy, it is characterised by the same pattern of IgG deposition as diabetic nephropathy on immunofluorescence microscopy, with a granular glomerular capillary deposition of C3; hence, the absence of C3 glomerular capillary staining is an important negative feature in diabetic nephropathy. Staining for both κ and λ light chains is usually present, and is an important feature to rule out monoclonal immunoglobulin deposition disease (light-chain deposition disease, and light-chain and heavy-chain deposition disease).

Electron microscopy features

The earliest ultrastructural abnormality in diabetic nephropathy is diffuse thickening of the GBM¹³ (fig 4A), which progressively increases as the disease advances. Several biochemical changes occur and contribute to increased GBM thickness in diabetic nephropathy, principally an increase in collagen type IV deposition and impairment of excess extracellular matrix degradation.¹⁴ A variable degree of mesangial expansion by extracellular matrix deposition and increased mesangial cellularity can be present (fig 4B). There is a reduction in podocyte

Figure 2 Diabetic nephropathy. (A) Mild diffuse expansion of mesangium in early diabetic nephropathy (periodic acid Schiff (PAS) stain). (B) Diffuse thickening of the glomerular basement membrane (GBM) (PAS stain). (C) Sclerotic nodule (Kimmelstiel-Wilson nodules) in early nodular diabetic nephropathy (PAS stain). (D) Marked glomerular lobular accentuation in advanced nodular diabetic nephropathy (PAS stain). (E) The glomerular lobulation is highlighted by silver stain. (F) Fibrin cap is characteristic for diabetic nephropathy. It is caused by insudation and accumulation of plasma proteins between the glomerular endothelium and the GBM (PAS stain). (G) Afferent and efferent arteriolar hyalinosis is characteristic for diabetic nephropathy (PAS stain).

number (podocytopenia), with a reduced podocyte per glomerulus ratio, even in diabetes of short duration.^{15 16} This is associated with foot process effacement. Areas of hyalinosis appear electron dense, and are often present in sclerotic areas, and must be differentiated from immune-complex deposits (fig 4C). Non-specific mesangial fibrils (diabetic fibrillosis) are occasionally present in sclerotic nodules and are probably

secondary to chronic mesangial injury. Diabetic fibrillosis should be distinguished from fibrillar glomerulonephritis and amyloidosis. Congo red negativity, negative or non-specific immunofluorescence, localisation to the mesangium in a segmental fashion, and more bundle-like than random arrangement of fibrils are helpful features to differentiate non-specific diabetic mesangial fibrillar deposition from

Figure 3 Immunofluorescence microscopy in diabetic nephropathy shows linear staining of immunoglobulin G along the glomerular basement membranes.

amyloidosis and fibrillar glomerulopathy.¹⁷ Box 1 summarises the light microscopic, immunofluorescence and ultrastructural features of diabetic nephropathy.

MORPHOLOGICAL DIFFERENTIAL DIAGNOSIS

In both diffuse and nodular diabetic glomerulosclerosis, clinicopathological correlation with a history of diabetes mellitus is essential for accurate diagnosis. The differential diagnosis of diffuse diabetic glomerulosclerosis is wide and includes immune-complex glomerulonephritis such as IgA nephropathy/Henoch–Schönlein purpura, lupus glomerulonephritis, membranoproliferative glomerulonephritis (MPGN) and membranous glomerulonephritis (table 1). Most of these conditions are readily distinguished from diabetic nephropathy

Box 1: The pathological features and renal complications of diabetic nephropathy

- Light microscopic
 - Mesangial expansion
 - Diffuse glomerular basement membrane thickening
 - Nodular glomerulosclerosis (Kimmelstiel–Wilson nodules)
 - Mesangiolysis and glomerular microaneurysms
 - Fibrin cap
 - Capsular drop
 - Afferent and efferent hyaline arteriosclerosis
 - Interstitial fibrosis and tubular atrophy
 - Interstitial mononuclear inflammatory cell infiltrate
 - Acute pyelonephritis
 - Papillary necrosis
- Immunofluorescence
 - Linear staining of the glomerular basement membrane and tubular basement membrane for immunoglobulin (Ig) G and albumin
 - Non-specific staining for IgM and C3 in sclerotic nodules
 - Variable staining of both κ and λ light chains
- Electron microscopy
 - Mesangial expansion by matrix and increased mesangial cellularity
 - Diffuse GBM thickening
 - Diabetic fibrillosis
 - Podocytopenia
 - Diffuse foot process effacement
 - Electron-dense areas of hyalinosis in sclerotic nodules

Figure 4 Ultrastructural findings in diabetic nephropathy. (A) Diffuse thickening of the GBM and absence of immune-type dense deposits. (B) Expansion of the mesangium due to marked increase in mesangial matrix causes sclerotic nodules in diabetic nephropathy. (C) Note the subendothelial hyalinosis. This should not be confused with immune-complex deposits.

Table 1 Differential diagnosis of diffuse diabetic glomerulosclerosis

Disease	IF	EM
IgAN/HNP	Predominant or codominant mesangial staining for IgA with or without C3	Mesangial expansion due to electron-dense deposits and increased mesangial matrix and cellularity, rare subendothelial and epithelial and intramembranous deposits
MGN	Granular GBM staining for IgG and C3 + variable staining for IgM and IgA, mesangial staining in secondary disease (eg, lupus nephritis) Diffuse granular GBM and mesangial staining for C3 with or without IgG and IgM	Diffuse or segmental subepithelial and intramembranous electron-dense deposits, projection of the GBM between deposits (spikes reaction on light microscopy silver stain), and diffuse effacement of foot processes Type I MPGN Granular subendothelial electron-dense deposits with or without mesangial deposits, mesangial interposition and GBM splitting Type II MPGN Interrupted or continuous electron-dense material within the lamina densa with or without mesangial deposits Subepithelial, subendothelial and mesangial electron-dense deposits and endothelial tubuloreticular inclusions
MPGN (type I and II)*	Full house pattern of multiple immunoglobulin deposition and complement components	

EM, electron microscopy; GBM, glomerular basement membrane; HNP, Henoch-Schönlein purpura; IF, immunofluorescence; IgAN, IgA nephropathy; LN, lupus nephritis; MGN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; TBM, tubular basement membrane.

*Can also cause nodular glomerulosclerosis.

Table 2 Differential diagnosis of nodular diabetic glomerulosclerosis*

Disease	IF	EM
Renal amyloidosis	Staining for κ or λ light chains in the mesangium, GBM, tubulointerstitium and blood vessel wall	Randomly oriented, non-branching amyloid fibrils, 8–12 nm in diameter
MIDD	LCDD Linear staining of the GBM, TBM and vascular wall basement membranes with monoclonal light chain ($\kappa > \lambda$) HCDD Linear staining of the GBM and vascular wall basement membranes of predominantly IgG γ -heavy chain	Continuous band of electron-dense granular, powdery deposits in the inner aspect of the GBM, mesangial nodules and outer aspect of the TBM (in LCDD)
Cryoglobulinaemia glomerulosclerosis	Mesangial and GBM staining for IgM, IgG and C3	Mesangial, subendothelial and subepithelial electron-dense deposits, intracapillary thrombi and leucocytic infiltrate
FG	Deposition of polyclonal IgG (with γ -1 and γ -4 restriction) and C3	Mesangial and GBM deposition of randomly oriented, non-branching fibrillar deposits, 16–24 nm in diameter
ITG	Deposition of monoclonal IgG with κ or λ light-chain restriction in the mesangium and GBM	Mesangial, subendothelial, intramembranous and subepithelial deposition of microtubules with hollow centres, 20–50 nm in diameter, arranged in organised parallel arrays
ING	Linear staining of the GBM and TBM for IgG and albumin	Mesangial expansion, diffuse GBM thickening, visceral epithelial foot processes effacement

EM, electron microscopy; FG, fibrillar glomerulonephritis; GBM, glomerular basement membrane; HCDD, heavy-chain deposition disease; IF, immunofluorescence microscopy; Ig, immunoglobulin; ING, idiopathic nodular glomerulosclerosis; ITG, immunotactoid glomerulonephritis; LCDD, light-chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; TBM, tubular basement membrane.

*Table 1 describes the immunofluorescence and ultrastructural features of membranoproliferative glomerulonephritis.

by light microscopy and ultrastructural evaluation. On the light microscopic level, arteriolar hyalinosis is usually less severe than in diabetic nephropathy, and it affects the afferent arterioles with sparing of the efferent arterioles.

The differential diagnosis of nodular diabetic glomerulosclerosis includes diverse conditions such as chronic idiopathic and secondary MPGN type I and II, amyloidosis, monoclonal immunoglobulin deposition disease, fibrillar and immunotactoid glomerulopathies, fibronectin glomerulonephritis, mixed cryoglobulinaemia, idiopathic nodular glomerulosclerosis, hypertensive nephropathy and Takayasu arteritis (table 2). These entities can usually be easily distinguished from diabetic nodular glomerulosclerosis. Difficult cases require meticulous histopathological examination and the utilisation of immunofluorescence and electron microscopy diagnostic tools, and good clinical correlation.

Chronic idiopathic or secondary type I MPGN is characterised by diffuse and global mesangial expansion, intense endocapillary proliferation, and lobular accentuation with diffuse thickening of the GBM, which exhibits double contouring that is readily identified on PAS and methenamine silver stains¹⁸ (fig 5A). Immunofluorescence shows diffuse granular glomerular capillary loop and mesangial staining of C3, with or without staining for IgG and IgM. Ultrastructurally, widespread

mesangial and subendothelial electron-dense deposits are present (fig 5B). In type II MPGN (dense deposit disease), the light microscopic and immunofluorescence microscopy features are similar to type I MPGN, but ultrastructurally, the disease is characterised by the presence of large, intramembranous, often discontinuous electron-dense deposits.¹⁹

Renal amyloidosis is usually associated with systemic amyloidosis, and is characterised by the deposition of Congo red positive, acellular, eosinophilic proteinaceous material that shows a characteristic apple-green birefringence under polarised light in the mesangium, GBM, tubulointerstitium and blood vessels (fig 6A,B). There is deposition of β -pleated amyloid fibril, usually of amyloid light chain (AL) or amyloid associated (AA) types. The morphological appearance of renal amyloidosis shows a wide spectrum of changes. It ranges from only minimal mesangial expansion to massive amyloid deposits, with a non-proliferative, non-inflammatory nodular glomerulosclerosis. The staining quality on PAS is typically paler than the mesangial matrix in diabetic glomerulosclerosis. In amyloid light chain, immunofluorescence typically shows staining for either κ or λ light chain, and absence of staining for immunoglobulin heavy chains. Electron microscopy shows the characteristic aggregates of randomly oriented, non-branching amyloid fibrils that measure 8–12 nm in diameter

Figure 5 Membranoproliferative glomerulonephritis. (A) Diffuse mesangial expansion and glomerular lobular accentuation can resemble diabetic nephropathy (periodic acid Schiff stain). (B) Subendothelial immune-complex dense deposits.

(fig 6C). Foot process effacement overlying portions of the glomerulus with amyloid deposition is commonly present.²⁰

Renal non-amyloidotic monoclonal immunoglobulin deposition disease (MIDD) is characterised by antibody light-chain or heavy-chain deposits within the GBM, renal TBM and blood vessels. MIDD encompasses three related subtypes depending on the deposited immunoglobulin components: light-chain deposition disease, heavy-chain deposition disease and mixed light-chain and heavy-chain deposition disease.²¹ MIDD is usually but not always associated with plasma cell dyscrasias. By light microscopy, all subtypes share similar histological features. The most common histological finding is nodular glomerulosclerosis, which can not be distinguished from classic diabetic nodular glomerulosclerosis^{21–23} (fig 7A). Some subtle light microscopic features, such as a regular distribution of the sclerotic nodules in a given glomerulus, positivity of PAS stain and negative methenamine silver stain in the sclerotic nodules (table 3), can be of some help to differentiate MIDD from diabetic glomerulosclerosis by light microscopy. In addition, the TBM is thickened by a characteristic deposition of ribbon-like

refractile, eosinophilic PAS-positive material.²² Immunofluorescence is essential for definitive diagnosis of MIDD; depending on the subtype of MIDD, there is a diffuse, linear staining of the GBM and TBM with monoclonal immunoglobulin light or heavy (or mixed) chains (fig 7B). In most cases of light-chain deposition disease, the deposits are composed of κ light chain (κ to λ ratio 9:1),²⁰ and in cases of heavy-chain deposition disease, IgG γ -heavy chain is predominant.^{24–25} Ultrastructural examination of MIDD shows a continuous band of electron-dense granular-powdery deposits in the inner aspect of the GBM (fig 7C), in the mesangial nodules, and particularly in cases of light-chain deposition disease, in the outer aspect of the TBM. A variable degree of irregular thickening and wrinkling of the GBM, and foot process effacement is usually present.

Cryoglobulins are defined as circulating immunoglobulins that precipitate when the serum is incubated at a temperature of $<37^{\circ}\text{C}$ and re-dissolve on warming. Cryoglobulinaemia is classified into three types. Type I cryoglobulinaemia is characterised by the presence of a pure monoclonal immunoglobulin, typically either IgM or less often IgG, and usually is

Figure 6 Renal amyloidosis. Amyloidosis can involve all the renal histological compartments (A) glomeruli and arterioles (periodic acid Schiff stain), (B) interstitial arteries (PAS stain). (C) Ultrastructurally, the amyloid fibres are randomly oriented, non-branching and measure 8–12 nm in diameter.

Figure 7 Light-chain deposition disease (LCDD). (A) Nodular glomerular sclerosis is the commonest morphological pattern in LCDD and can be indistinguishable from nodular diabetic nephropathy by light microscopy (periodic acid Schiff stain). (B) Immunofluorescence shows linear staining of κ light chain in the glomeruli and the tubular basement membrane. (C) Electron microscopy shows a continuous band of electron-dense glomerular deposits in the inner aspect of the glomerular basement membrane.

associated with multiple myeloma, Waldenström's disease and other lymphoproliferative disorders. Mixed cryoglobulinaemia (type II and type III) is characterised by the presence of more than one class of immunoglobulins. Type II cryoglobulinaemia is the most common type and is characterised by the presence of immune complexes that contain complexes of monoclonal IgM with rheumatoid factor activity, and polyclonal IgG. Type III cryoglobulinaemia is characterised by the presence of immune complexes formed by more than one polyclonal immunoglobulin (usually polyclonal IgM with rheumatoid factor activity and polyclonal IgG).²⁶ Both types II and III cryoglobulinaemia are associated with a variety of clinical disorders, mainly hepatitis C virus infection, and autoimmune disorders. Cryoglobulinaemic glomerulonephritis is found in 25–35% of patients with cryoglobulinaemia.^{20–27} The most common histological pattern for renal injury is a membranoproliferative glomerulonephritis, with lobular accentuation and nodular glomerulosclerosis in chronic cases.²⁸ The presence of intracapillary proliferation, prominent intracapillary monocytic

inflammatory cell infiltrates, homogenous PAS-positive cryoglobulin deposits and double contouring (tram-track appearance) of the GBM are helpful morphological features to distinguish cryoglobulinaemic glomerulonephritis from diabetic nodular glomerulosclerosis. Immunofluorescence microscopy shows the presence of the IgM, IgG immunoglobulins and C3 within the cryoglobulin deposits. Electron microscopy shows the presence of mesangial and subendothelial deposits as well as capillary luminal cryoglobulin thrombi and prominent leucocytic infiltrates.

Fibrillar glomerulonephritis and immunotactoid glomerulonephritis are two closely related entities, characterised by Congo red-negative fibrillar deposits. Both diseases have diverse morphological patterns, and may present as a diffuse proliferative or membranoproliferative glomerulonephritis, and marked mesangial expansion with lobular accentuation and nodular glomerulosclerosis resembling nodular diabetic nephropathy (fig 8A). Immunofluorescence and electron microscopy are important for accurate diagnosis and to separate these entities from other causes of nodular sclerosis. Fibrillar glomerulonephritis is ultrastructurally characterised by the mesangial and GBM deposition of randomly oriented, non-branching fibrillar deposits that range from 16 to 24 nm in diameter. On immunofluorescence microscopy, these deposits are found to be composed predominantly of polyclonal IgG, with γ -1 and γ -4 isotype restriction, and C3.²⁹ In immunotactoid glomerulonephritis, the fibrillar deposits can be intramembranous, subepithelial, subendothelial and in the mesangium, contain larger microtubular structures with hollow centres, which typically range in measurement from 20 to 50 nm,^{29–30} and are arranged in organised parallel arrays (fig 8B). Immunofluorescence evaluation shows predominant deposition of monoclonal IgG with κ or λ light-chain restriction in the mesangium and along glomerular capillary loops.³¹ Fibronectin glomerulopathy is a rare autosomal dominant disease,

Table 3 Utilisation of histochemical stains in the differential diagnosis of nodular glomerulosclerosis

Disease	Special stains		
	PAS	Silver	Congo red
DN	+	+	—
ING	+	+	—
Amyloid	—	—	+
MIDD	+	—	—
FG and ITG	+(weak)	+	—
FNG	+	—	—

DN, diabetic nephropathy; FG, fibrillar glomerulonephritis; FNG, fibronectin glomerulopathy; ING, idiopathic nodular glomerulosclerosis; ITG, immunotactoid glomerulopathy; MIDD, monoclonal immunoglobulin deposition disease; PAS, periodic acid Schiff.

Figure 8 Immunotactoid glomerulonephritis. (A) Note the focal glomerular lobulation, hyalinosis and diffuse thickening of the glomerular basement membrane (periodic acid Schiff stain). (B) Large microtubular structures characteristic for immunotactoid glomerulonephritis.

characterised by marked mesangial expansion due to massive deposition of fibronectin, and prominent hypocellular lobular accentuation of the glomerular tufts (fig 9A). The glomerular nodules are PAS-positive, but silver and Congo red stains are negative (fig 9B). Ultrastructurally, fibronectin glomerulopathy is characterised by large mesangial and subendothelial electron-dense deposits (fig 9C); the deposits are granular, with or without fibrillar substructures. Glomerular immunoperoxidase expression of fibronectin is essential for diagnosis (fig 9D).³²⁻³³

Idiopathic nodular glomerulosclerosis (ING) is an unusual distinct clinicopathological entity with light microscopic and ultrastructural features similar to those of nodular diabetic glomerulosclerosis, but without evidence of abnormal glucose metabolism.³⁴⁻³⁵ It is strongly associated with smoking and long-standing hypertension.³⁶ On light microscopy, ING is characterised by glomerulomegaly, nodular mesangial glomerulosclerosis (fig 10), hyaline afferent and efferent arteriolar sclerosis, arterial sclerosis, and a variable degree of interstitial fibrosis and tubular atrophy. Capsular drops, a lesion once

thought specific for diabetic nephropathy, can also be seen. Immunofluorescence shows linear staining of GBM and TBM for IgG and albumin, and absence of immune deposits. Ultrastructurally, there is mesangial matrix expansion, diffuse GBM thickening and visceral epithelial foot process effacement. There are no electron-dense or fibrillar deposits. Immunoperoxidase for endothelial antigens shows a different mesangial vascularisation pattern in ING not seen in diabetic nephropathy. Absence of diabetes mellitus after a detailed clinical history and investigations, and the exclusion of other causes of nodular glomerulosclerosis are prerequisite to diagnose ING, as the morphological findings are identical to those seen in diabetic nephropathy.

CONCLUSION

Diabetic nephropathy is a common clinical problem that is often encountered in renal biopsy, and morphologically characterised by diffuse and nodular glomerulosclerosis. Immunofluorescence and electron microscopy studies are

Figure 9 Fibronectin glomerulonephritis. (A) Mildly hypercellular lobulated glomerular tufts (periodic acid Schiff stain). (B) In comparison with diabetic nephropathy, silver stain is negative in fibronectin glomerulopathy. (C) Electron microscopy shows large subendothelial electron-dense deposits. (D) Immunoperoxidase glomerular staining for anti-fibronectin antibody.

Figure 10 Idiopathic nodular glomerulosclerosis. The nodular mesangial glomerulosclerosis is histologically indistinguishable from nodular diabetic nephropathy.

Take-home messages

- A typical case of diabetic nephropathy shows diffuse or nodular mesangial matrix increase, glomerular basement membrane thickening and arteriolar hyalinosis. Other findings can include fibrin caps, capsular drops, and capillary microaneurysms.
- There are many mimics of diabetic nephropathy and a complete assessment of light microscopy, immunofluorescence and electron microscopy is required to rule out other diseases that appear similar.
- Always correlate the biopsy findings with the clinical history. If the patient is not diabetic, consider the diagnosis of idiopathic nodular glomerulosclerosis.

essential to differentiate diabetic nephropathy from other conditions that can produce diffuse and nodular glomerulosclerosis, and can lead to a misdiagnosis of diabetic nephropathy. Close clinicopathological correlation is mandatory for accurate diagnosis of diabetic nephropathy, as the patient should either be diabetic or show evidence of abnormal glucose metabolism.

It is also important to distinguish secondary changes as a consequence of diabetic nephropathy from another renal disease in addition to diabetic nephropathy. This situation most commonly arises when a patient with diabetes develops nephrotic-range proteinuria and renal biopsy shows diabetic nephropathy and segmental glomerulosclerosis. Although it is tempting to diagnose idiopathic focal segmental glomerulosclerosis in addition to diabetic nephropathy, most cases with this pattern of injury are best explained as secondary segmental glomerulosclerosis as a complication of diabetic nephropathy.

As ING cannot be distinguished from diabetic nephropathy by routine light microscopy, immunofluorescence and electron microscopy, diabetic nephropathy should never be diagnosed without supportive clinical information.

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