CHAPTER 1
Pattern of Glomerular Lesions

Normal Glomeruli by Light Microscopy

- Minimal change disease (MCD)
- Thin basement membrane nephropathy (TBMN)

Case: A 42-year-old man with a history of mild hypertension presents with serum creatinine of 2.2 mg/dL and proteinuria of 9.2 g/day.

Renal Biopsy Findings

Light microscopy (LM): All glomeruli appear unremarkable with patent peripheral capillary lumina and no mesangial expansion (Jones silver, Figure 1-1).

Immunofluorescence (IF): No specific staining identified.

Electron microscopy (EM): There is extensive foot-process effacement with microvillous transformation of visceral epithelial cells. The glomerular basement membrane is unremarkable, and there are no deposits (Figures 1-2 and 1-3).

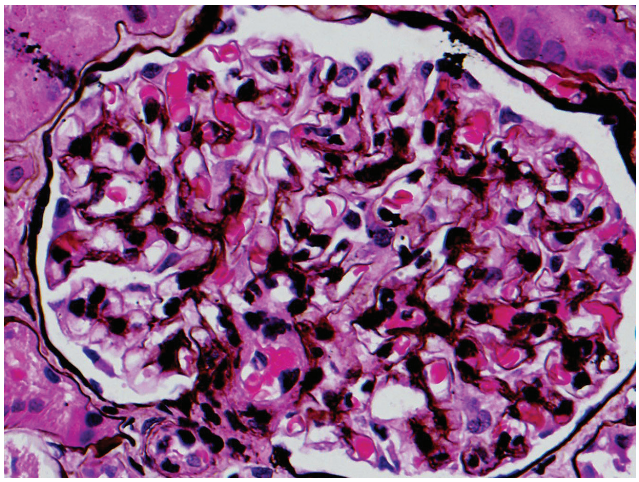


Figure 1-1

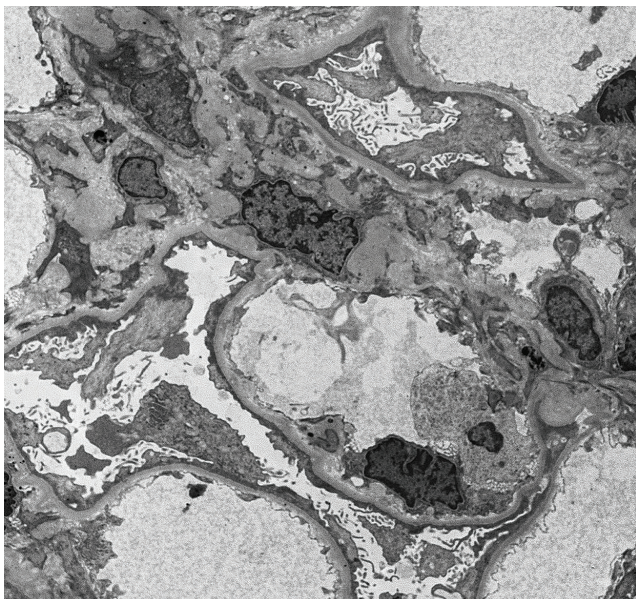


Figure 1-2

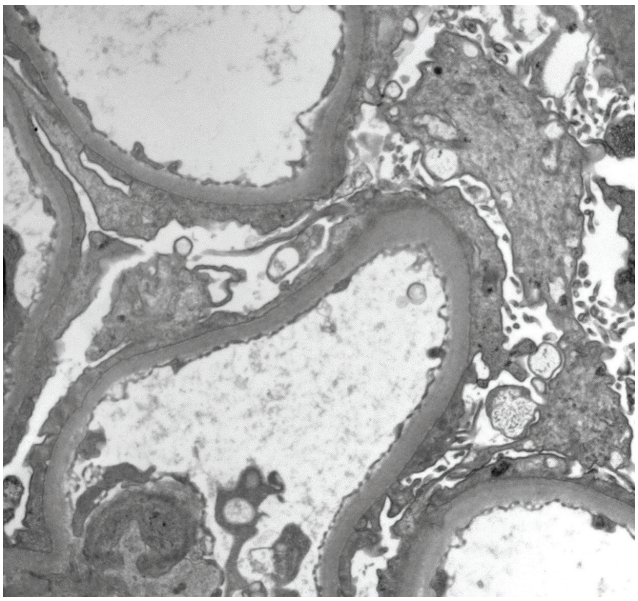


Figure 1-3

Diagnosis: Minimal Change Disease (MCD)

Key Diagnostic Morphologic Features:

Extensive, often complete, foot-process effacement by EM and no segmental sclerotic lesions by light microscopy. Of note, the biopsy should contain an adequate number of glomeruli, ie, ≥25, in total, to exclude the possibility of unsampled focal segmental glomerulosclerosis (FSGS).

Salient Clinical Features:

MCD typically presents as the nephrotic syndrome, and it is the most common cause of nephrotic syndrome in children. The majority of cases respond to corticosteroids; therefore, in children the biopsy is performed only when the proteinuria is unresponsive to corticosteroid therapy or clinical features suggest another etiology. In adults, MCD accounts for 10% to 15% of nephrotic syndrome. MCD does not cause progressive renal insufficiency. If present, often in adults, as in this case, it is related to underlying chronic renal disease, eg, essential hypertension. Most cases of MCD in children are primary or idiopathic. Secondary MCD is more common in adults and may be seen in association with Hodgkin disease, non-Hodgkin lymphoma, malignant thymoma, renal cell carcinoma, graft-versus-host disease in bone marrow transplantation, and drugs like lithium and nonsteroidal anti-inflammatory drugs (NSAIDs). The occurrence of acute interstitial nephritis along with MCD is characteristically seen with NSAIDs.

The pathogenesis of MCD is a mystery; however, association with hypersensitivity reactions, such as with drugs or bee stings, points toward immune dysfunction as an initiating factor.

Case: A 23-year-old woman presents with a history of microscopic hematuria, mild proteinuria (<0.5 g/day), and serum creatinine of 0.7 mg/dL.

Renal Biopsy Findings

Light microscopy: All glomeruli appear unremarkable with patent peripheral capillary lumina and no mesangial expansion (periodic acid-Schiff–hematoxylin [PASH] Figure 1-4).

Immunofluorescence: No significant staining for immunoglobulins or complements identified.

Electron microscopy: There is widespread thinning of the glomerular basement membrane (GBM) with nearly intact foot processes (Figure 1-5). The basement membrane measures 170 nm to 294 nm, with an average thickness of 220 nm (Figure 1-6).

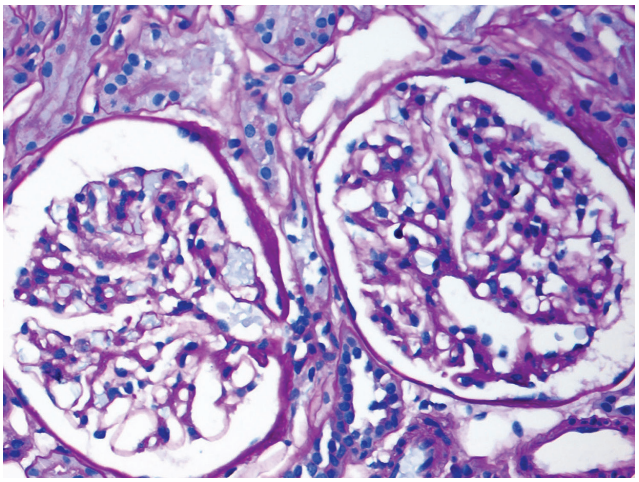


Figure 1-4

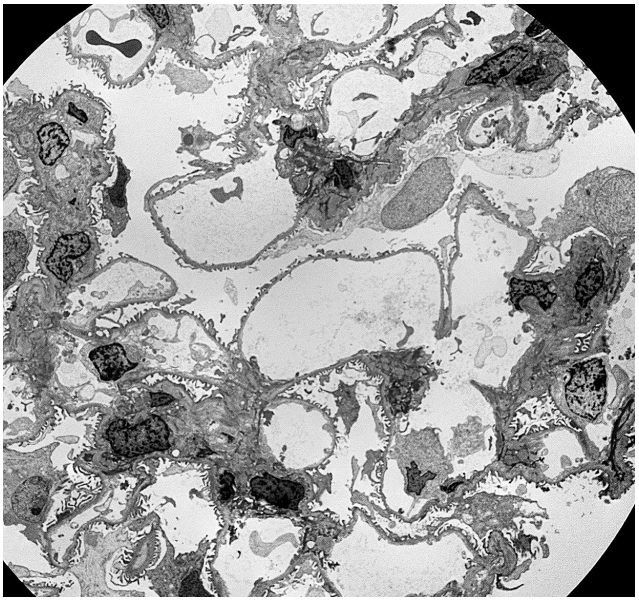


Figure 1-5

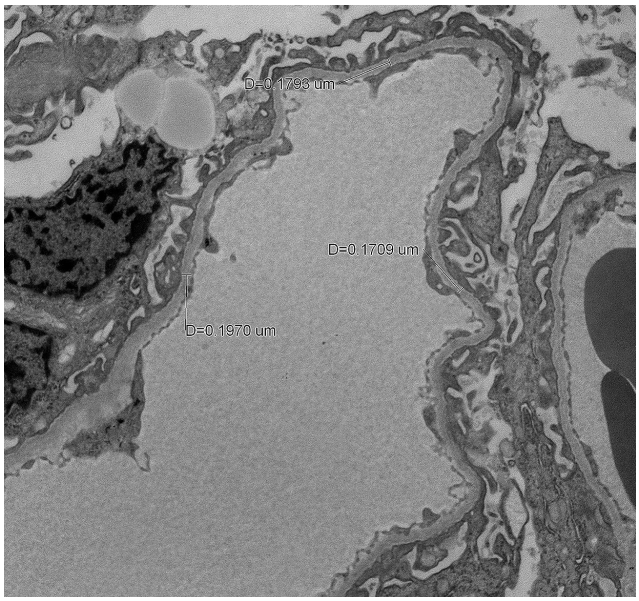


Figure 1-6

Diagnosis: Thin Basement Membrane Nephropathy (TBMN)

Key Diagnostic Morphologic Features:

Widespread thinning of the glomerular basement membrane by EM. Diagnosis of TBMN is made specifically by measurements of the EM images and must be compared with the normal for age, as GBM thickness normally increases from childhood to adulthood (the World Health Organization [WHO] considers thin GBM with average ≤250 nm in adults and <180 nm in children). However, the relative thickness of the base of intact foot process versus the GBM gives an approximate guide to the GBM thickness. In the adult, the normal GBM is two to three times the thickness of the base of the normal foot process of the podocyte.

Salient Clinical Features:

TBMN is a lesion of type IV collagen, associated with heterozygous mutation in the COL4-α3 and COL4-α4 genes, inherited in an autosomal dominant pattern. It initially was considered a nonprogressive hereditary disorder with no significant clinical consequence, termed *benign familial hematuria.* However, some cases are progressive, and about 40% of the patients with TBMN indeed represent a heterozygous carrier state of autosomal recessive Alport syndrome. TBMN is common, estimated to occur in >1% of the population. It usually presents with persistent asymptomatic microscopic hematuria, occasionally with isolated episodes of macroscopic hematuria. Renal function is normal in most cases; however, up to 30% of cases develop late onset renal insufficiency or hypertension. Nonnephrotic range proteinuria is common. Occasionally, nephrotic range proteinuria may occur, and biopsy in such patients usually shows superimposed FSGS. Recent genetic studies from these patients have shown additional genetic abnormalities, particularly involving podocyte proteins.

Proliferative Glomerular Lesions

- Nodular mesangial expansion with or without proliferation
  - Diabetic nephropathy (DN)
  - Light chain deposition disease (LCDD)
  - Advanced membranoproliferative glomerulonephritis (MPGN)
  - Amyloidosis
  - Fibrillary glomerulonephritis (FGN)
  - Idiopathic nodular glomerulosclerosis (ING)

Case: A 72-year-old man with a history of diabetes and monoclonal gammopathy of undetermined significance (MGUS) with IgG lambda predominance presents with acute on chronic kidney injury. Serum creatinine has increased from 2.1 mg/dL to 2.4 mg/dL. Urinary protein-to-creatinine ratio of 1 with increased lambda light chains.

Renal Biopsy Findings

Light microscopy: There is marked nodular mesangial expansion that appears lamellated and mildly hypercellular, staining strongly for PASH (Figure 1-7) and silver (Figure 1-8). There is severe hyaline arteriolosclerosis involving both afferent and efferent arterioles (hematoxylin-eosin [H&E] Figure 1-9)

Immunofluorescence: There is a nonspecific staining for IgG and equally strong staining for albumin along glomerular basement membrane and tubular basement membrane (not shown). No monoclonal staining for light chains identified.

Electron microscopy: There is markedly increased mesangial matrix, and glomerular basement membranes are thickened (Figures 1-10 and 1-11). Reference value for normal GBM thickness in adult males is 355 nm plus or minus 75 nm in our laboratory. No immune complex deposits or fibrillary deposits identified.

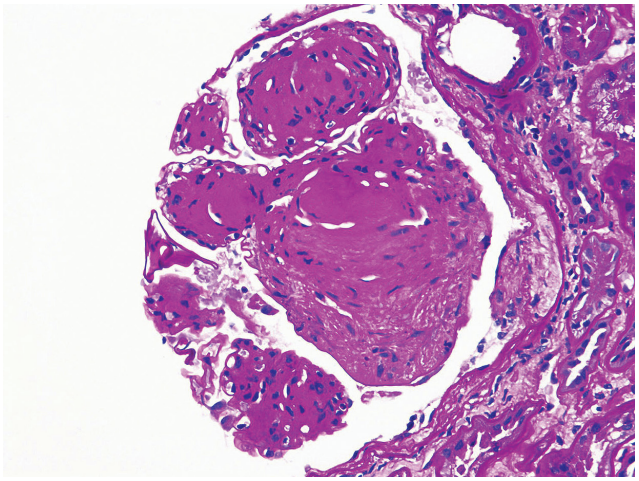
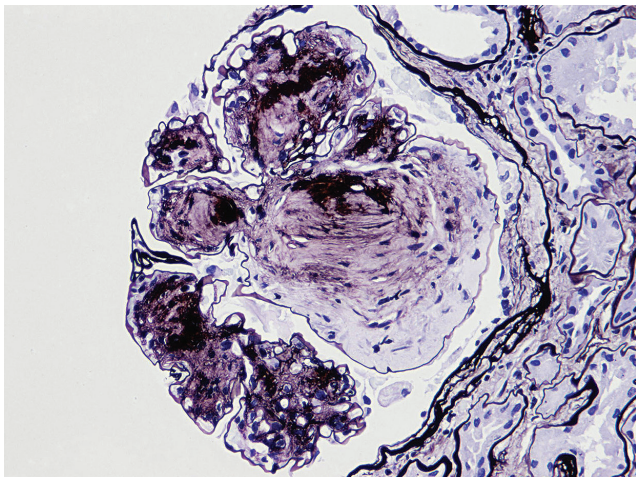


Figure 1-7

Diagnosis: Diabetic Nephropathy (DN)

Key Diagnostic Morphologic Features:

Three characteristic morphologic features are (1) lamellated, strongly PASH- and silver-positive, Congo red-negative nodules, known as Kimmelstiel-Wilson (K-W) nodules; (2) hyalinosis involving both afferent and efferent arterioles; and (3) thickened GBM by EM.



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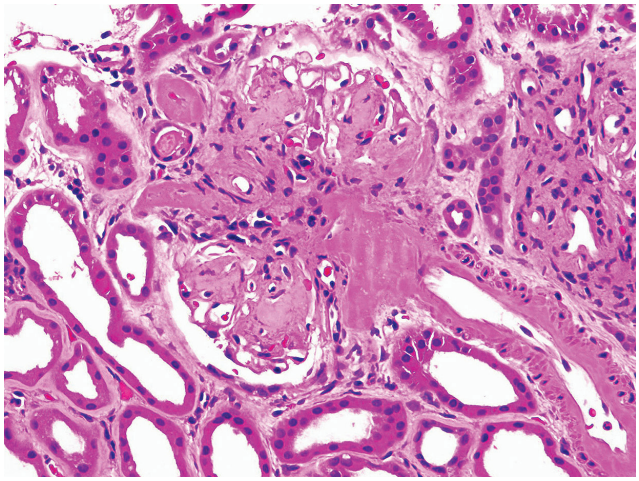

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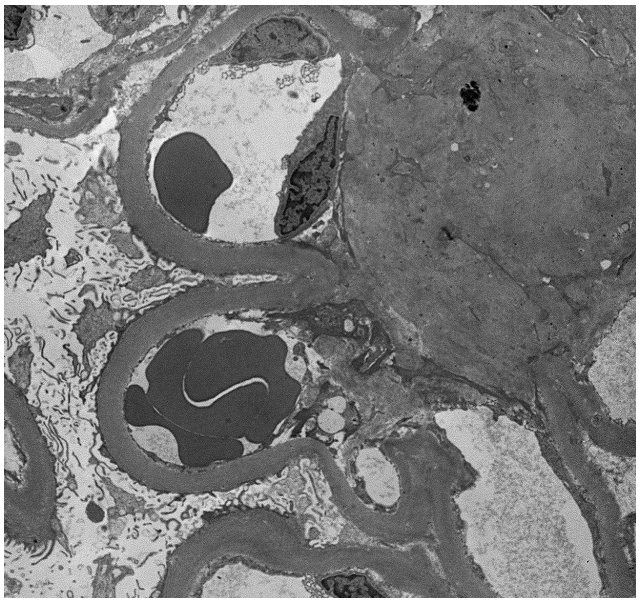


Figure 1-10

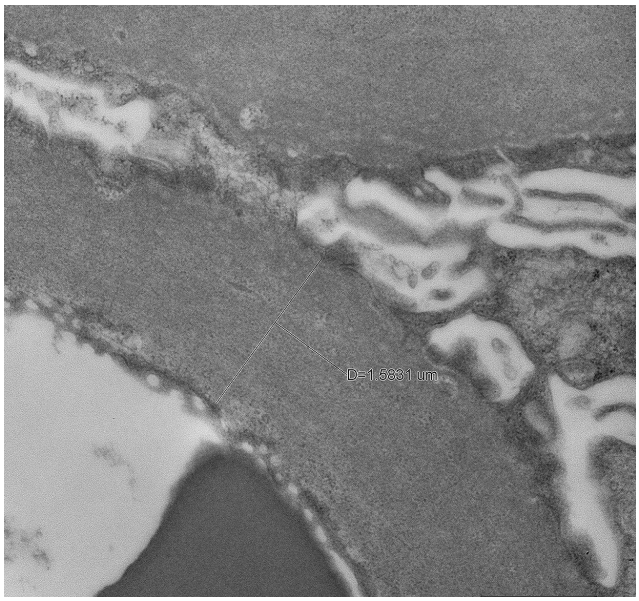


Figure 1-11

Salient Clinical Features:

DN is a clinical syndrome characterized by persistent albuminuria/proteinuria, a steady decline in renal function, and elevated blood pressure. It is the most common cause of end-stage renal disease (ESRD). It occurs in about 30% to 40% of diabetic patients with a longstanding history of diabetes, approximately 10 to 15 years. Patients with DN are usually not biopsied until there is some unusual clinical presentation, eg, acute renal failure or monoclonal proteinuria, as in this case. However, not all patients with monoclonal protein have related renal disease. In fact, a 2003 study by Paueksakon showed that the majority of patients with serum and/or urine monoclonal gammopathy who undergo renal biopsy had unrelated renal lesions. FSGS and diabetic nephropathy were the most common lesions found in those proteinuric patients.

Case: A 59-year-old man with a history of diabetes presents with 4+ proteinuria and abdominal distention due to severe ascites.

Renal Biopsy Findings

Light microscopy: There is marked nodular mesangial expansion with silver-negative (Figure 1-12) and weak PASH-positive (Figure 1-13), homogeneous, acellular material, also extending along the peripheral capillary loops. This acellular material in the glomerulus as well as associated arteriole shows green birefringence with a Congo red stain using polarized light (Figure 1-14).

Immunofluorescence: The glomerulus shows strong smudgy staining for lambda light chain in the same distribution as seen in LM (Figure 1-15). The staining for kappa light chain is completely negative (Figure 1-16).

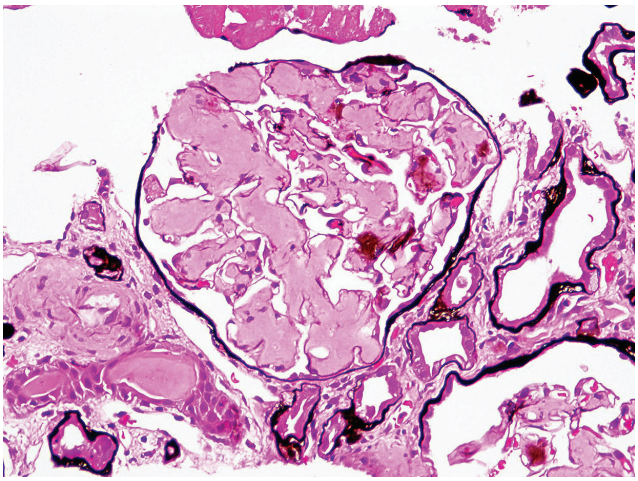
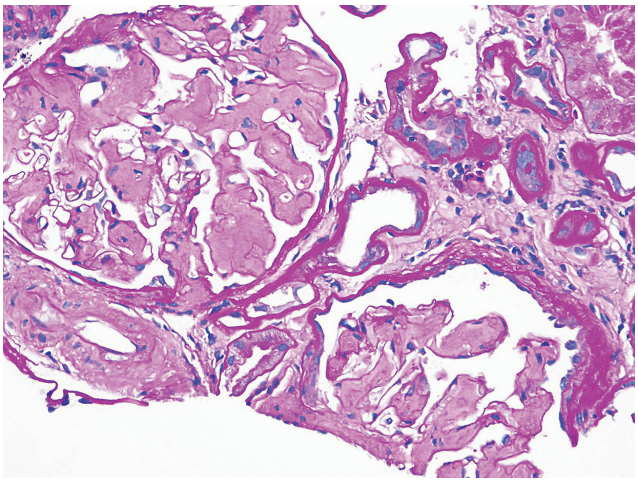


Figure 1-12



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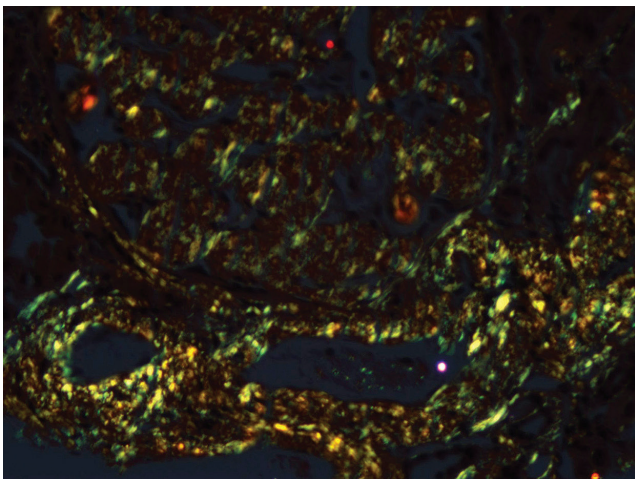

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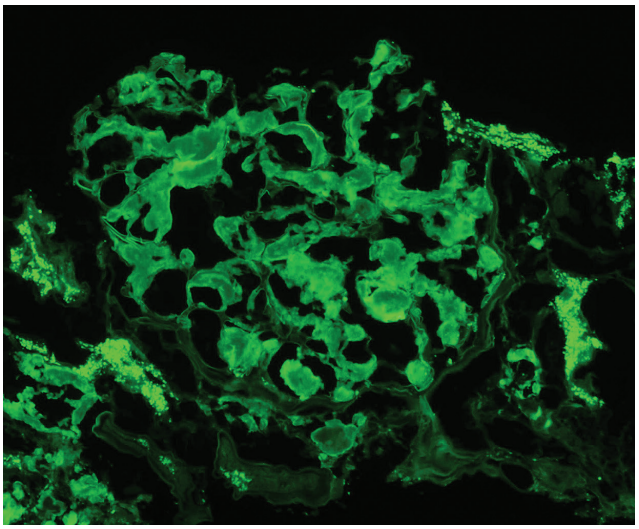

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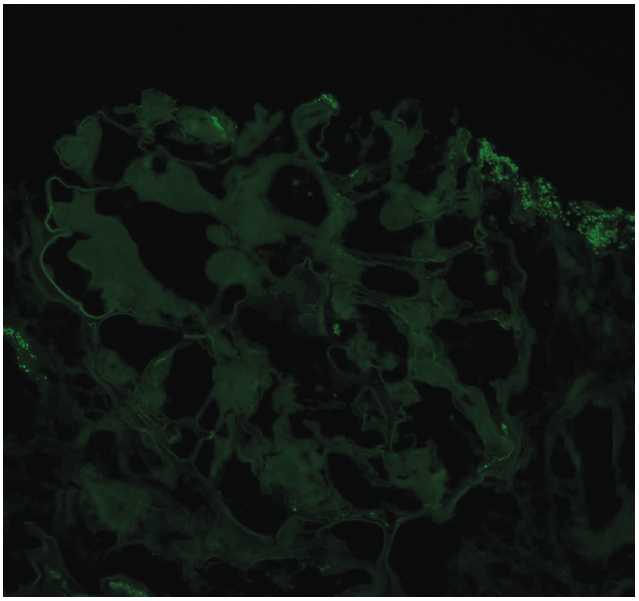


Figure 1-16

Electron microscopy: There is marked mesangial expansion with randomly arranged, nonbranching fibrillary deposits, ranging from 7 nm to 10 nm in diameter (Figures 1-17 and 1-18).

Diagnosis: Lambda AL (Amyloid Light Chain) Amyloidosis

Key Diagnostic Morphologic Features:

Acellular, silver-negative, and weak PASH-positive nodules with cotton candy-like fluffy appearance on H&E. The nodules are Congo red positive. Monoclonal staining with kappa or lambda, if AL type, is noted by IF. Nonbranching fibrillary deposits (7-12 nm), similar to pick-up sticks spread over the ground, are seen on EM examination.

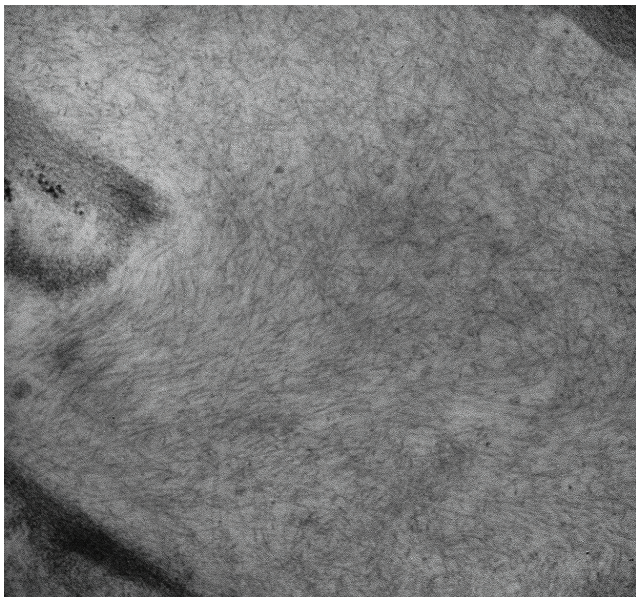


Figure 1-17

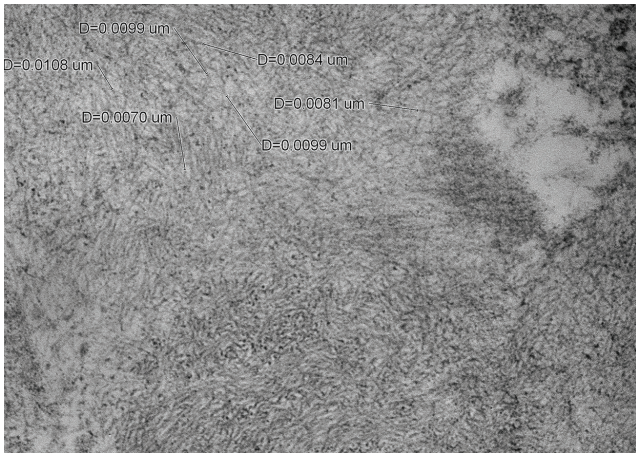


Figure 1-18

Salient Clinical Features:

AL amyloidosis is the most common type of amyloidosis in the United States, associated with plasma cell dyscrasia and lymphoproliferative malignancies, followed by AA (amyloid associated) amyloidosis, associated with chronic infectious and noninfectious inflammatory conditions such as tuberculosis, chronic osteomyelitis, or rheumatoid arthritis. ALECT2 (leukocyte chemotactic factor 2-associated amyloidosis) is the third most common type; it commonly occurs in Hispanics. Other forms of renal amyloid are rare. Regardless of the type, renal involvement by amyloidosis most commonly presents as nephrotic range proteinuria with mild renal impairment. Nephrotic syndrome is present in more than two-thirds of the patients. AL amyloidosis is a systemic disease, with the heart being the most common extrarenal organ involved, followed by nerves. Urine electrophoresis may show an M-spike; however, immunofixation electrophoresis (IFE) is more sensitive for the detection of monoclonal proteins.

Case: A 74-year-old man presents with acute renal failure (serum creatinine 12.0 mg/dL), 3+ proteinuria, and 2+ hematuria. There is a clinical concern for pulmonary renal syndrome due to concurrent pulmonary infiltrates and sinus complaints.

Renal Biopsy Findings

Light microscopy: There is marked nodular mesangial expansion with mildly increased mesangial cellularity (H&E Figure 1-19). The nodules are strongly PASH positive (Figure 1-20) and variably silver positive, and have a vague lamellated appearance (Figure 1-21). The tubular basement membranes are markedly thickened (Figure 1-22).

Immunofluorescence: There is strong staining for kappa light chain along thickened tubular basement membranes, in the glomerulus along capillary basement membrane, and in the mesangium (Figure 1-23). The staining for lambda light chain is completely negative (Figure 1-24).

Electron microscopy: There are punctate, amorphous, granular deposits along the inner side of the glomerular

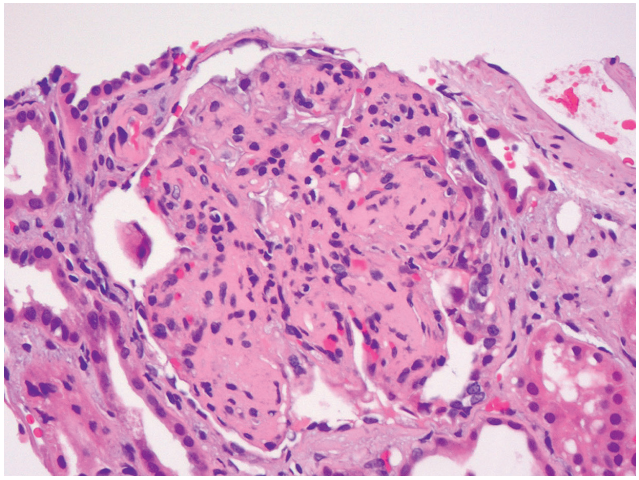


Figure 1-19

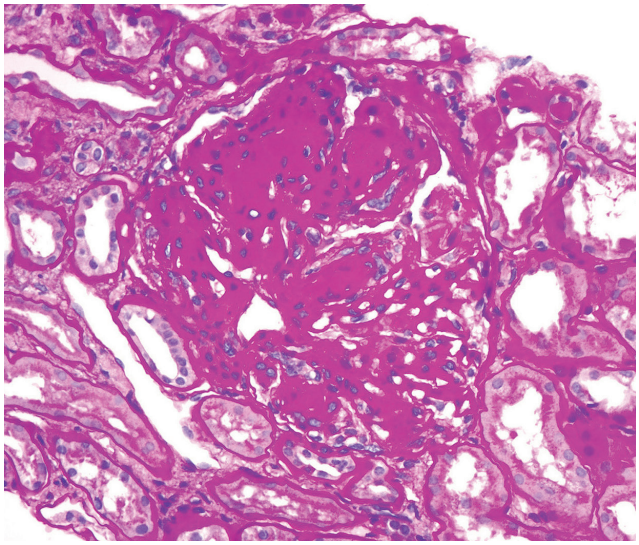


Figure 1-20

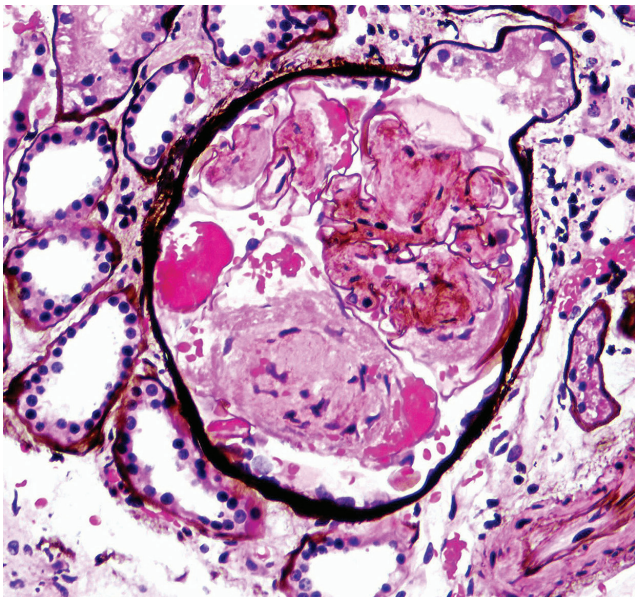
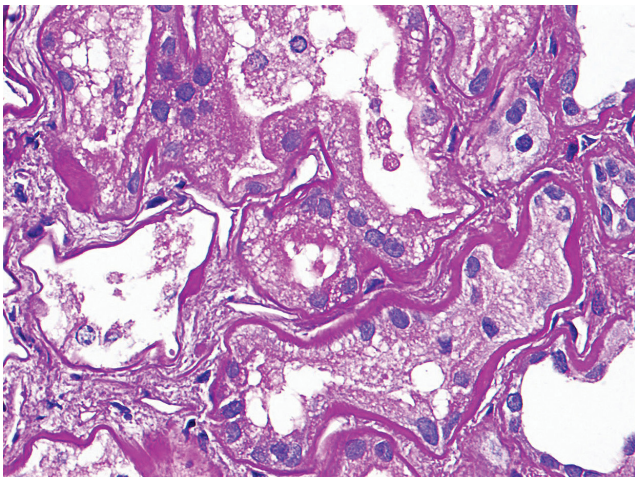


Figure 1-21



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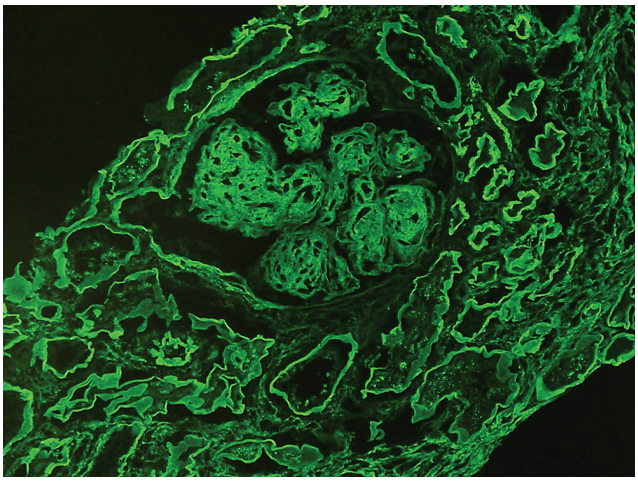

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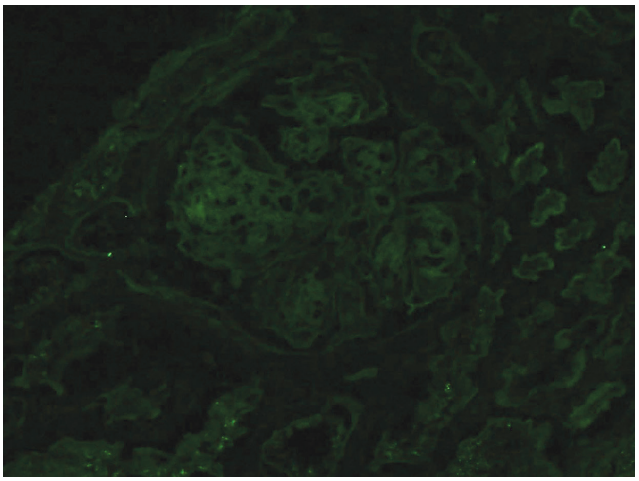

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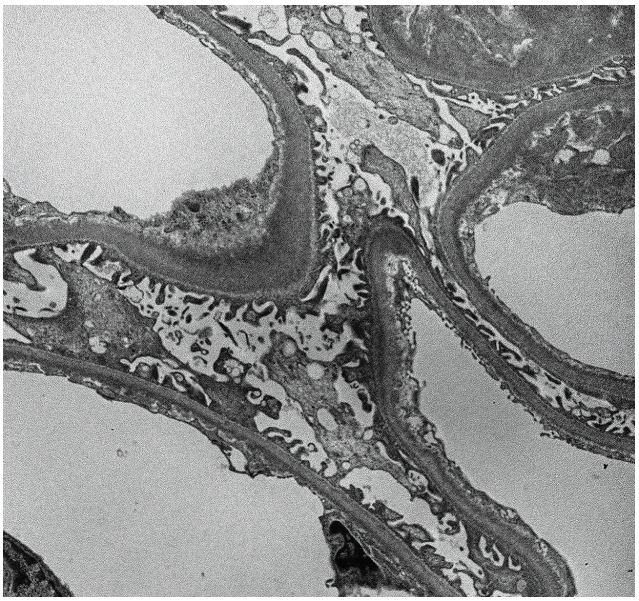


Figure 1-25

basement membranes (Figures 1-25 and 1-26) and outer side of tubular basement membranes (Figure 1-27).

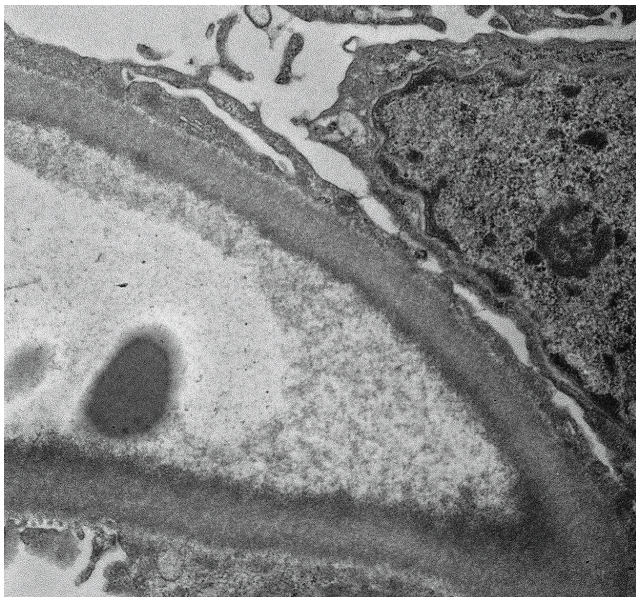
Diagnosis: Light Chain Deposition Disease (LCDD)

Key Diagnostic Morphologic Features:

PASH-positive, silver-negative to weak positive, Congo red-negative nodules, similar to K-W nodules of diabetic nephropathy by LM. Monoclonal staining by IF (mostly kappa, rarely lambda) in the glomeruli and along tubular basement membranes. Amorphous, punctate, electron-dense deposits along the inner side of glomerular basement membrane and outer side of tubular basement membrane by EM.

Salient Clinical Features:

LCDD typically presents with proteinuria, which is in the nephrotic range in about half of the patients, and varying degrees of renal dysfunction. In this case there was



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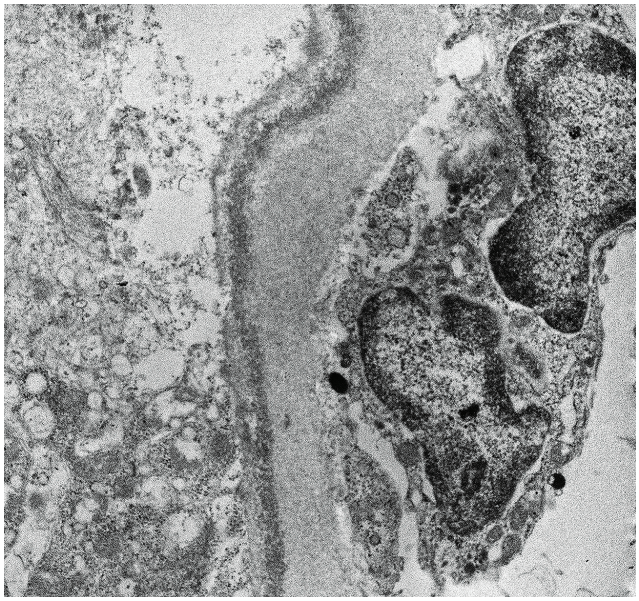


Figure 1-27

also associated light chain cast nephropathy (not shown), contributing to severe acute renal failure. The two diseases can rarely coexist. Follow-up bone marrow biopsy was diagnostic for multiple myeloma. However, most patients with LCDD have monoclonal gammopathy of undetermined significance (MGUS), instead of multiple myeloma, now termed *monoclonal gammopathy of renal significance (MGRS)*. Of note, renal biopsy findings indicative of a monoclonal process often precedes other clinical evidence of dysproteinemia. LCDD predominantly affects kidneys but also commonly involves the heart and liver. The renal outcome remains uncertain and depends on how early in its course the disease is detected.

Case: A 65-year-old man presents with 4+ proteinuria and hematuria.

Renal Biopsy Findings

Light microscopy: There is moderate to marked mesangial expansion in a vaguely nodular pattern showing variegated staining with silver stain (Figure 1-28) and weak staining with PASH (Figure 1-29), as well as mildly increased mesangial cellularity. A Congo red stain is negative (not shown).

Immunofluorescence: There is strong but smudgy mesangial as well as capillary loop staining for IgG (Figure 1-30), C3 (Figure 1-31), and light chains (not shown).

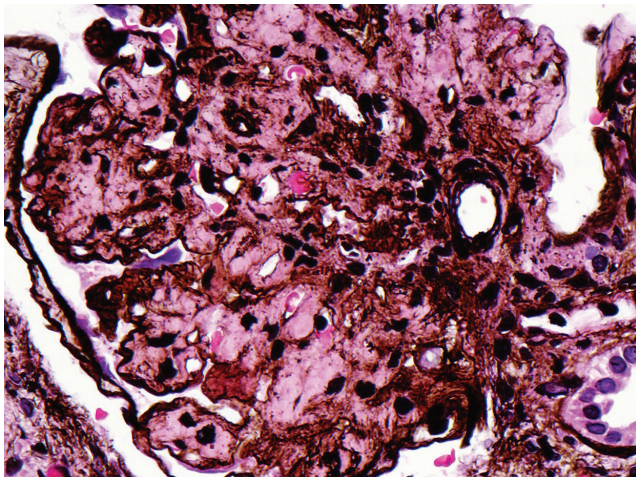
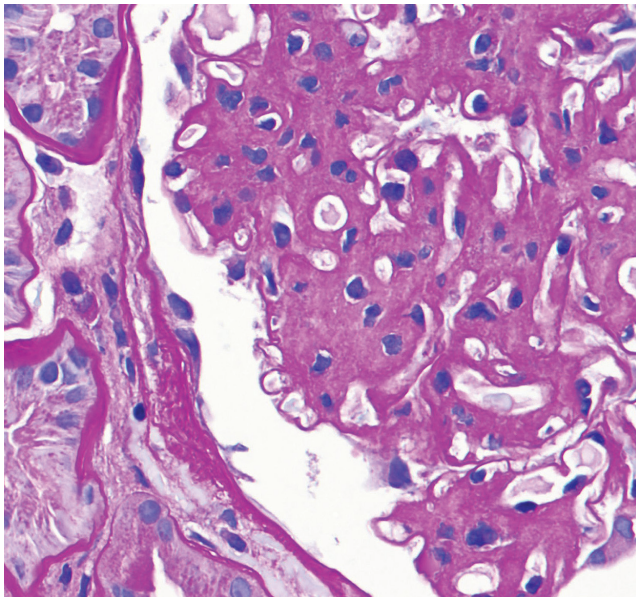


Figure 1-28



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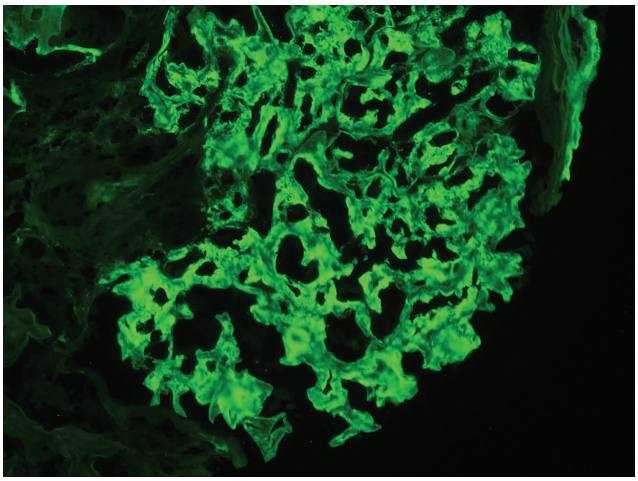

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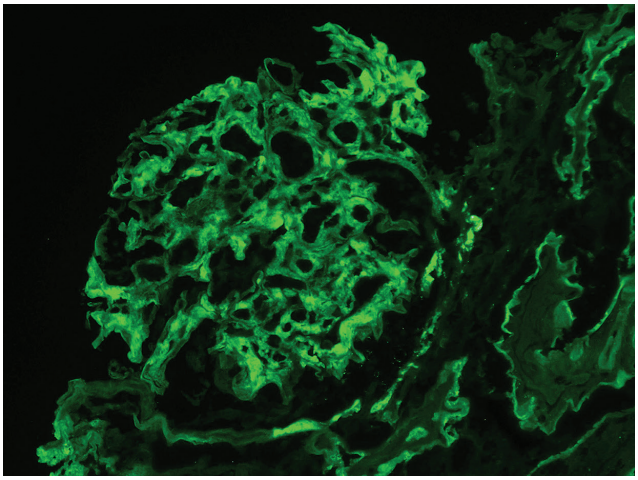

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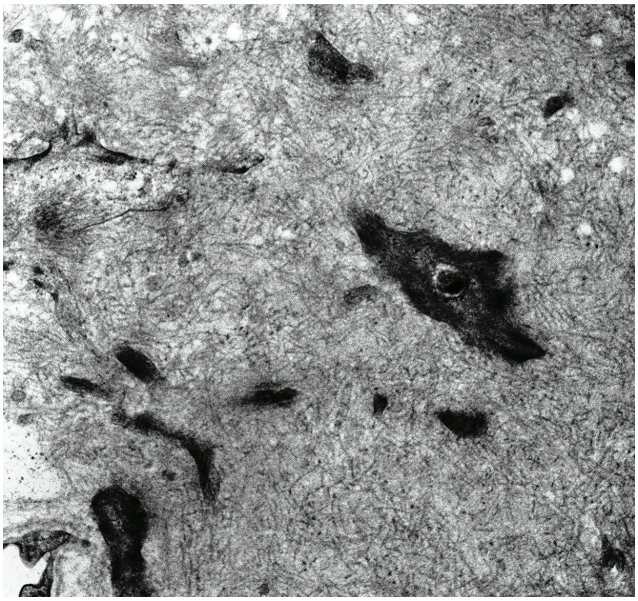

Figure 1-32

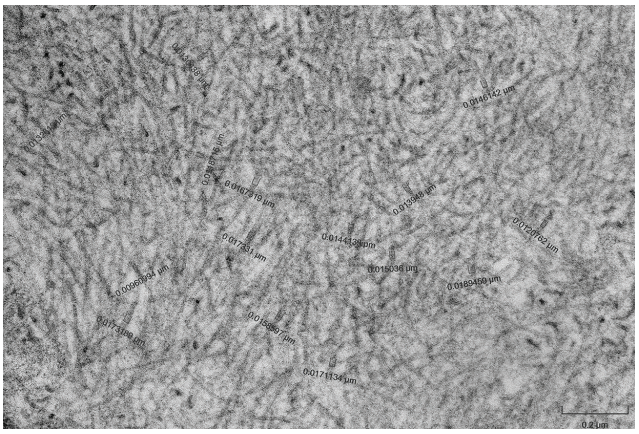

Figure 1-33

Electron microscopy: There is mesangial expansion with nonbranching, randomly arranged fibrillary deposits, similar to amyloid. However, these fibrils are relatively larger in size, about 9 nm to 18 nm in diameter (Figures 1-32 and 1-33).

Diagnosis: Fibrillary Glomerulonephritis (FGN)

Key Diagnostic Morphologic Features:

Vaguely nodular mesangial expansion staining weakly positive for PASH and silver; however, silver stain may be negative. Congo red negative. Strong smudgy staining with IgG (usually polyclonal) and C3 by IF, and randomly arranged, nonbranching fibrillary deposits (12-20 nm) by EM.

Salient Clinical Features:

Fibrillary glomerulonephritis is an unusual lesion. Patients typically present with proteinuria, usually in the nephrotic range, and most also have microscopic hematuria. Although it has been reported in association with a variety of systemic diseases, including lymphoproliferative malignancy, carcinoma, and hepatitis C, the vast majority of cases are idiopathic. A recent study by Andeen et al based on laser microdissection-assisted liquid chromatography-mass spectrometry has shown a novel proteomic biomarker for FGN: DNAJB9, a member of the chaperon gene family. DNAJB9 is overexpressed not only in idiopathic cases, but also in cases associated with hepatitis C virus infection, autoimmune diseases, and malignancy, and can be detected by immunohistochemistry. No definite treatment is available for FGN. Unfortunately, about 50% of patients develop end-stage renal failure within 4 years of diagnosis. The disease recurs in transplants.