

A 58-Year-Old Man with Diabetes Mellitus and Nephrotic Syndrome

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CASE PRESENTATION

A 58-year-old man with a 13-year history of type 2 diabetes mellitus visits a walk-in clinic because of increasing swelling in his lower extremities. The swelling began approximately 6 months previously and has worsened over the past 6 weeks. The patient reports no intercurrent illnesses and specifically denies any fever, chills, arthralgias, joint swelling, or skin rash. Additionally, he reports no visual changes, epistaxis, hemoptysis, or cough. He has no symptoms of flank pain, hematuria, dysuria, or darkening of the urine.

The patient's medical history is significant for hypertension, type 2 diabetes mellitus, and an appendectomy. His medications include glyburide 10 mg daily, amlodipine 10 mg daily, and ibuprofen occasionally. He does not abuse alcohol, tobacco, or illicit drugs. No family history of kidney disease is present, although several of his family members have diabetes mellitus and heart disease.

Physical examination reveals a healthy-appearing man in no acute distress. The patient's blood pressure is elevated at 152/93 mm Hg. His heart rate is 75 bpm, respiratory rate is 14 breaths/min, and temperature is 37.3°C (99.1°F). Examination of the head and neck is unremarkable, with no evidence of conjunctivitis, lymphadenopathy, thyromegaly, or nasal ulceration. Examination of the fundi is notable for preproliferative diabetic retinopathy. The lungs are clear, but examination of the heart is remarkable for an S₄ gallop. Findings on abdominal examination are benign, with no hepatosplenomegaly or palpable masses. The lower extremities have 3+ pitting edema up to the midcalf. No skin rash, petechiae, or purpura is present. A neurologic examination is noncontributory, with no focal findings or motor or sensory changes. Initial laboratory data for the case patient are shown in [Table 1](#).

The patient's chest radiograph shows no infiltrate, effusion, or adenopathy. Based on the findings of edema, high-grade proteinuria, hypoalbuminemia, and lipiduria, nephrotic syndrome is suspected. A 24-hour urine

collection confirms nephrotic proteinuria (4.35 g of protein). Work-up for secondary or systemic causes of his renal disease is performed, revealing no antinuclear or anti-double-stranded antibodies, normal complement and rheumatoid factor levels, negative serology for hepatitis B and C, and no serum cryoglobulins. Analysis of serum and urine protein and immunoelectrophoresis reveal no immunoglobulins or free light chains. A renal biopsy is also performed. Light microscopic evaluation of the kidney tissue ([Figure 1](#)) is notable for mesangial nodules (ie, Kimmelstiel-Wilson nodules), diffuse thickening of capillary loops, and glomerulosclerosis.

- **What is the most likely cause of the patient's renal disease?**
 - A) Diabetic nephropathy
 - B) Focal and segmental glomerulonephritis
 - C) Light-chain deposition disease
 - D) Membranous glomerulonephritis
 - E) Minimal change disease

- **What is the most appropriate treatment?**
 - A) Administer more amlodipine for better control of blood pressure
 - B) Begin insulin therapy for better glycemic control
 - C) Initiate therapy with an angiotensin-converting enzyme inhibitor
 - D) Restrict dietary protein to 0.6 g/kg body weight per day
 - E) Strongly recommend a low-cholesterol diet

ANSWERS

The correct answers are diabetic nephropathy (A) and begin insulin therapy for better glycemic control (B).

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Table 1. Results of Initial Laboratory Testing in the Case Patient

Serum chemistries

Albumin, 2.9 g/dL
Chloride, 101 mEq/L
Creatinine, 1.4 mg/dL
Potassium, 4.1 mEq/L
Sodium, 132 mEq/L
Total carbon dioxide, 24 mEq/L
Total cholesterol, 255 mg/dL
Urea nitrogen (blood), 24 mg/dL

Hematologic findings

Leukocyte count, $8 \times 10^3/\text{mm}^3$
Hematocrit, 37.2%
Hemoglobin, 11.9 g/dL
Hemoglobin A_{1c}, 7.1%
Platelet count, $185 \times 10^3/\text{mm}^3$

Urinary findings

Erythrocytes, 10–15
Leukocytes, none
Protein, 4.35 g/dL
Hyaline casts, few

DISCUSSION

The findings seen on microscopic evaluation of the kidney tissue (Figure 1) are consistent with a diagnosis of diabetic nephropathy. A normal glomerulus is shown in Figure 2 for comparison. Table 2 identifies the common causes of nephrotic syndrome in a middle-aged patient. Renal biopsy is not always required to diagnose diabetic nephropathy. In the absence of relevant clinical findings (eg, rash, joint abnormalities, hemoptysis) or laboratory parameters (eg, presence of antinuclear antibodies, low complement levels, erythrocyte casts) suggestive of a systemic illness, examination of renal tissue in a diabetic patient with retinopathy, proteinuria, and renal insufficiency is unnecessary. On rare occasions, other renal lesions may develop in patients with diabetic nephropathy, leading to “double nephropathies.”

EPIDEMIOLOGY

Diabetic nephropathy is the leading cause of end-stage renal disease in the United States. The cumulative incidence of nephropathy (ie, proteinuria) in patients with type 1 or type 2 diabetes mellitus is approximately 40% after a 40-year history of the disease. The annual

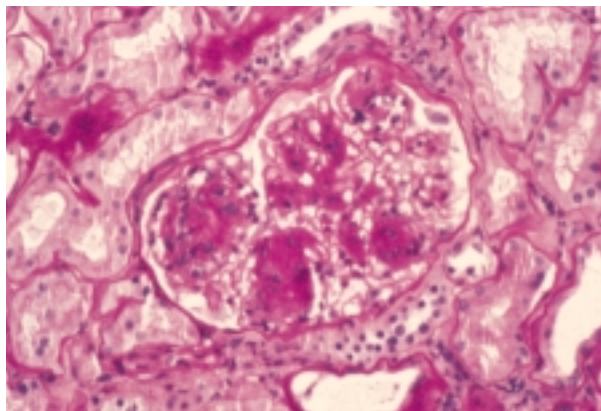


Figure 1. Photomicrograph of a renal biopsy specimen obtained from the case patient. Kimmelstiel-Wilson nodules, diffuse thickening of capillary loops, and glomerulosclerosis are present.

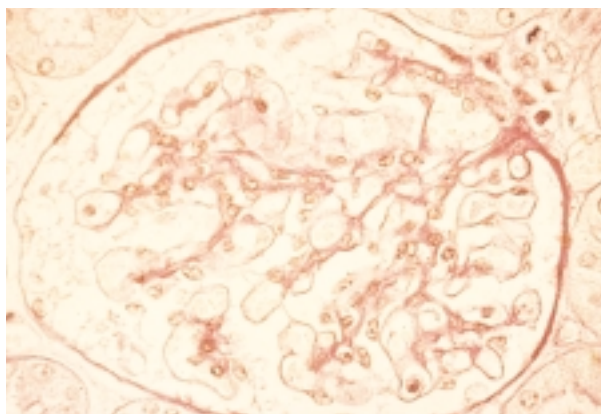


Figure 2. Photomicrograph of a renal biopsy specimen showing a normal glomerulus.

incidence, however, peaks before a patient has had diabetes mellitus for 20 years. Thereafter, the risk of developing nephropathy declines. Some populations are at a greater risk for developing diabetic nephropathy, including African Americans, Mexican Americans, American Indians, and Polynesians.

PATHOLOGY

Pathologic changes characteristic of diabetic nephropathy can be artificially divided into 5 stages. At the onset of diabetes mellitus, a patient’s renal histology shows no abnormalities. Within 2 to 3 years (stage I), subtle glomerular basement thickening occurs. After 3 to 8 years (stage II), further glomerular basement thickening and mild mesangial matrix widening develop. Incipient diabetic nephropathy (stage III) is noted

at 8 to 15 years and is clinically evident with the onset of microalbuminuria (30–300 mg/24 hours, or > 20 µg/min). Renal histology reveals further glomerular capillary basement membrane thickening, mesangial widening, and intracapillary glomerulosclerosis (ie, glomerular scar formation). Overt diabetic nephropathy (stage IV), associated with macroalbuminuria (> 300 mg/24 hours) and renal dysfunction, occurs after 15 to 29 years. As seen in the case patient, advanced glomerular basement membrane thickening and mesangial widening, Kimmelstiel-Wilson nodules, arteriolar hyalinization, and glomerulosclerosis are noted on renal biopsy. In addition, altered structure of blood vessels (hyalinosis) and tubulointerstitium (tubular atrophy and interstitial fibrosis) is noted. End-stage renal failure (stage V) from diabetes mellitus occurs after 20 to 30 years and is characterized by glomerular capillary closure and sclerotic and hyalinized glomeruli (ie, scarred kidneys).

TREATMENT

The major therapeutic interventions to slow the progression of diabetic nephropathy to end-stage renal disease involve improved glycemic control and antihypertensive therapy. Screening patients with diabetes mellitus for microalbuminuria and proteinuria will facilitate early identification and treatment of diabetic nephropathy. The Diabetes Control and Complication Trial revealed that strict glycemic control, measured as mean hemoglobin A_{1c} of 7% (versus conventional control with mean hemoglobin A_{1c} of 9%), reduced incipient and overt diabetic nephropathy. Strict glycemic control was associated with a reduction in the development of micro- and macroalbuminuria in both the primary and secondary cohorts studied.¹

Aggressive control of blood pressure also plays an important role in reducing the progression of diabetic nephropathy.^{2–4} Lowering the blood pressure to a level below 130/80 mm Hg may help to blunt glomerular injury by reducing the transmission of systemic arterial pressure to the glomerulus.

The use of angiotensin-converting enzyme inhibitors—and angiotensin receptor antagonists in patients with type 2 diabetes mellitus—clearly slows the progression to end-stage renal failure in patients with diabetic nephropathy through multiple effects: reducing glomerular capillary pressure, causing antagonism of direct effects of angiotensin II on the development of glomerulosclerosis and interstitial fibrosis, and potentially increasing the beneficial effects of nitric oxide in the kidney.^{5–8}

Table 2. Causes of Nephrotic Syndrome

Idiopathic

Focal glomerulosclerosis
 Membranous GN
 Mesangial proliferative GN
 Mesangiocapillary GN
 Minimal change GN

Secondary causes

Amyloidosis
 Diabetic nephropathy
 Light-chain deposition disease
 Secondary focal glomerulosclerosis
 HIV, certain medications, renal ablation, obstructive uropathy, obesity
 Secondary membranous GN
 Infection, certain medications, cancer, autoimmune disorders
 Secondary mesangiocapillary GN
 Infection, drug abuse, cancer, autoimmune disorders
 Secondary minimal change GN
 Infection, certain medications, cancer

GN = glomerulonephritis.

Although controversial, moderate dietary protein restriction (0.6 to 0.8 g/kg daily) may also slow the decline in renal function in patients with diabetic nephropathy.⁹ Other potentially beneficial but currently unproven treatments for diabetic nephropathy include the use of lipid-lowering statins and the inhibition of both aldose reductase and advanced glycosylation end-product formation.¹⁰ Smoking cessation may also reduce the progression of diabetic nephropathy. **HP**

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