

Case Study: Renal Disease in Type 1 Diabetes

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Presentation

C.M. is a 27-year-old woman with type 1 diabetes diagnosed at age 14 when she presented with diabetic ketoacidosis. Her initial insulin treatment was complicated by poor glycemic control, frequent hypoglycemia, and weight gain.

Two years ago, she developed hypertension, which was treated with hydrochlorothiazide, 25 mg daily. At that time, she was noted to have nonproliferative diabetic retinopathy. Blood urea nitrogen (BUN) was 23 mg/dl, creatinine was 0.9 mg/dl, and dipstick urinalysis was negative for protein.

She now presents with accelerated hypertension (172/108 mmHg) and pitting edema of the legs to the level of the knees. Urinalysis reveals 3+ protein and 2+ blood. Urine microscopic analysis reveals hyalin and red blood cell casts. BUN is 37 mg/dl; creatinine is 1.5 mg/dl; and 24-h urine reveals 9.7 g of protein. Creatinine clearance is 58 ml/min. Total cholesterol is 279 mg/dl.

Questions

1. Does C.M. have diabetic nephropathy?
2. What diagnostic tests are indicated?
3. What is the appropriate treatment for C.M.'s renal disease?

Commentary

We believed that C.M. had type 1 diabetes with nonproliferative retinopathy, accelerated hypertension, and nephrotic syndrome. Although the history of retinopathy and hypertension were consistent with the development of diabetic nephropathy, the urinary findings and rapid progression of renal insufficiency were inconsistent with diabetic nephropathy and raised the specter of a second etiology of her renal disease.

On further testing, Westergren erythrocyte sedimentation rate was 81

mm/h, urine immunoelectrophoresis was negative for Bence Jones protein, and rheumatoid factor was negative, but anti-nuclear antibody was positive in a titer of 1:320 with a homogenous pattern. Anti-DNA was 5.1% (normal 0–7%). C3 complement was low, C4 complement was normal, and CH 50 was at the lower limit of normal. Renal biopsy demonstrated mixed proliferative and focal membranous glomerulonephritis consistent with lupus nephropathy. In addition, changes were present suggestive of early diabetic glomerulosclerosis.

The patient was treated with monthly intravenous cyclophosphamide (Cytosan) for 6 months and was subsequently maintained on prednisone and hydroxychloroquine (Plaquenil). Serum creatinine peaked at 2.0 mg/dl, but over the next 2 years it fell to 1.3 mg/dl. Urine protein excretion fell to 0.85 g/24 h.

Approximately 40% of people with longstanding type 1 diabetes develop diabetic nephropathy. Essentially all patients with diabetic nephropathy have diabetic retinopathy detectable by dilated retinal examination.

In type 1 diabetes, diabetic nephropathy follows a predictable course from onset of diabetes to the onset of microalbuminuria to frank nephropathy to end-stage renal disease or death. Microalbuminuria develops 10–14 years after onset of diabetes. Without treatment, clinical nephropathy follows within 5 years, and azotemia develops ~5 years later. Hypertension develops in association with microalbuminuria and progresses with diabetic nephropathy. In diabetic nephropathy, the urine sediment is bland. Red blood cells are usually absent, although they may be present with infection or in the rare instance of papillary necrosis. Red cell casts are absent.

Diabetic nephropathy is a diagnosis of exclusion. In this case, accelerated hypertension, an active urinary sediment with both red cells and red cell casts, and the rapid onset of nephrotic syndrome with renal insufficiency is more consistent with glomerulonephritis mediated by immune mechanisms. Thus, thorough testing for secondary causes of immune-mediated glomerulonephritis, including renal biopsy, were indicated to identify a second, more treatable, cause of renal disease.

Attributing the patient's renal disease to diabetic nephropathy, failing to pursue alternative diagnoses, and thus failing to implement disease-specific treatment would have likely resulted in the rapid onset of renal failure.

Clinical Pearls

1. In type 1 diabetes, diabetic nephropathy is a diagnosis of exclusion.
2. The absence of diabetic retinopathy, onset of microalbuminuria before 10 years, and onset of clinical nephropathy before 15 years, along with findings of an active urinary sediment with red cell casts and rapidly progressive renal insufficiency, should prompt further evaluation.
3. Establishing an alternative diagnosis is critical when alternative disease-specific therapies exist.

Suggested Readings

Molitch ME: Management of early diabetic nephropathy. *Am J Med* 102:392–398, 1997

Golbus J, McCune WJ: Lupus nephritis: classification, prognosis, immunopathogenesis, and treatment. *Rheum Dis Clin North Am* 20:213–242, 1994

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