CASE REPORT

Gaucher Disease With Nephrotic Syndrome: Response to Enzyme Replacement Therapy

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Nephrotic syndrome in patients with Gaucher disease is rare; most of the few reported cases have had a well-defined glomerulopathy often with Gaucher cells in the glomeruli. We report the case of a 54-year-old woman with Gaucher disease, who had splenectomy at age 25, preeclampsia with renal biopsy disclosing only endotheliosis at age 32, and improvement of proteinuria and reappearance of heavy proteinuria (7.2 g/24 h) at age 41. Renal biopsy disclosed Gaucher cells in glomeruli and interstitium. The patient did not receive therapy specifically for glomerular disease. Enzyme replacement, begun 4 years later and maintained until now, was associated with amelioration of systemic symptoms and virtual disappearance of proteinuria with a follow-up of 10 years. This case apparently is the first instance of nephrotic syndrome consequent to Gaucher disease itself and successful treatment with specific enzyme replacement.

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INDEX WORDS: Gaucher disease; nephrotic syndrome.

Renal involvement in Gaucher disease is unusual in regard to clinical manifestations and morphologic abnormalities. Although Gaucher disease is the most common lysosomal storage disease, descriptions of important renal damage are scant; affected patients invariably have had splenectomy before the discovery of a kidney abnormality. The usual morphologic finding is the accumulation of Gaucher cells in the interstitium or in glomeruli, often as incidental features. Glomerular functional manifestations are rare and consist of varying degrees of proteinuria with or without renal insufficiency; only nine patients have been reported. We report the case of a patient with Gaucher disease and nephrotic syndrome who, after enzyme replacement, sustained a long-term remission. This case is of note because of the nature of the unusual presentation and response to therapy.

CASE REPORT

The patient is a 54-year-old woman who first was diagnosed with Gaucher disease at age 21, when she presented with anemia, thrombocytopenia, and splenomegaly; the last had been present since 4 years of age, but bone marrow examination was not done until the diagnosis was established at age 21. Because of progressive anemia and thrombocytopenia, she underwent splenectomy at age 25. Over the ensuing years, the patient developed significant bone involvement, pulmonary lesions with hypoxia, and increasing hepatomegaly. Gaucher disease had been diagnosed previously in her older brother, who died of hepatic failure at age 32, and in her mother at age 72, who died of carcinoma of the lung. The patient’s two children are alive and well.

At age 32 (1977) during a triplet pregnancy, the patient was discovered to have heavy proteinuria (7.0 g/24 h), with serum creatinine 1.0 mg/dL. Previous renal laboratory evaluation had revealed blood urea nitrogen, 9 mg/dL (creatinine clearance, 110 mL/min), and 1+ proteinuria at the time of splenectomy (age 25) and serum creatinine, 0.7 mg/dL, and 2+ proteinuria at age 31. Because of persistent heavy proteinuria, she underwent renal biopsy 5 weeks postpartum. For the next 8 years, renal function remained normal, and dipstick proteinuria was 1 to 2+. At age 41, because of reappearance of heavy proteinuria (7.2 g/24 h) and normal renal function (creatinine clearance, 103 mL/min), the patient underwent a second renal biopsy.

At age 45 (1990), the patient was begun on enzyme replacement therapy with alglucerase (Ceredase), 4,800 U every 2 weeks. Protein excretion was 5.6 g/24 h at that time. A ruptured cerebral berry aneurysm was surgically repaired the following year, with full neurologic recovery. At age 52, replacement therapy was changed to imiglucerase (Cerezyme), 4,800 U every 2 weeks. Since initiation of enzyme therapy, bone pain has decreased significantly, pulmonary function has improved, and hepatomegaly has lessened. Over the ensuing 10 years, although 24-hour determinations were not done, protein dipstick values, which were evaluated every year or so, decreased gradually from 4+ to 3+ to 2+ to 1+. As of October 2001, protein excretion was
measured at 300 mg/24 h, and creatinine clearance was 145 mL/min. At no time did the patient receive antihypertensives, corticosteroids, or other therapy, including angiotensin-converting enzyme inhibitors, specifically directed at the renal disease.

**Biopsy Findings**

The first biopsy specimen contained glomeruli only for electron microscopy; they were slightly enlarged with marked swelling of endothelial cells. There were lipid-containing monocytes in a few capillary lumina. Some capillary walls were thickened with subendothelial densities. The foot processes of epithelial cells were partially effaced, with large discrete stretches (Fig 1). There were no electron dense (immune complex) deposits in any location. Gaucher cells were not identified in glomeruli or in extraglomerular sites. These findings were indicative of preeclampsia.

The second biopsy specimen was characterized by several differences. There was adequate tissue for light microscopy, immunofluorescence, and electron microscopy, with cortex containing a total of 12 glomeruli. The most notable finding was the accumulation of Gaucher cells in lumina of several capillaries in approximately 50% of the glomeruli (Fig 2A). Similar cells also were in peritubular capillaries and in the interstitium (Fig 2B). The remainder of the glomerular structure was characterized by patent capillary lumina, single-contoured capillary walls, and minimal widening of mesangial regions without increased cellularity. Electron microscopy revealed the Gaucher cells to have large masses of accumulation of membrane-bound tubular structures consisting of fibrils 60 to 80 nm in diameter, often with a twisted arrangement (Fig 2C). The cells were in capillary lumina, occasionally directly apposed to basement membranes; some also extended into the mesangium. Capillary basement membranes were of normal thickness and appearance; peripheral migration and interposition of mesangium were in a few capillary walls in segments with accumulation of Gaucher cells. Rare small electron dense deposits were in mesangial regions in a few lobules in glomeruli with Gaucher cells. The foot processes of epithelial cells were largely effaced. Immunofluorescence disclosed segmental mesangial IgM and IgA in trace intensity and in a granular pattern.

![Fig 1. First biopsy specimen. Electron micrograph of representative glomerulus; endothelial cells are prominently swollen, and foot processes of visceral epithelial cells are discrete. (Original magnification × 14,400.)](image)

![Fig 2. Second biopsy specimen. (A) Glomerulus with clusters of Gaucher cells in capillary lumina (arrowhead). (Periodic acid–methenamine silver original magnification × 240.) (B) Similar cells are in the interstitium (arrowheads). (H&E, original magnification × 190.) (C) Electron micrograph of glomerular capillary filled with a Gaucher cell. Note intracellular microtubular structures (arrow). (Original magnification × 19,100.)](image)
DISCUSSION

Few reports of abnormal renal function in patients with Gaucher disease exist. The most common manifestation is of glomerular involvement, with varying degrees of proteinuria and hematuria. Although the pathologic features in all reported patients but one have included the presence of Gaucher cells in the glomeruli, some of the reports also described significant dense deposits by electron microscopy or granular deposits by immunofluorescence or well-defined glomerulopathies, such as membranoproliferative glomerulonephritis and focal and segmental glomerulosclerosis calling into question the role of Gaucher cells alone resulting in functional consequences. A few patients also were reported with nephrotic syndrome resulting from amyloidosis. Some published descriptions do not allow the reader to formulate a coherent morphologic understanding of the changes in the glomeruli in addition to the Gaucher cells. The present patient likely represents pure Gaucher cell–induced functional glomerular disease as judged by the glomerular morphology. The minor mesangial deposits of IgA and IgM (trace intensity by immunofluorescence) were likely of no pathologic or functional significance. The vast improvement in protein excretion and, to a small degree, improvement to normal renal function associated with specific replacement therapy argue that the cells with abnormal glycolipid storage may interfere with the glomerular filtration barrier; this is postulated solely on morphologic findings, however, without a likely physiologic explanation. In a similar vein, Newsom et al described a patient with a glycolipid storage disorder with features different from Gaucher disease but with heavy proteinuria and glomerular infiltration by the abnormal cells. As a result, these authors also suggested that the abnormal cellular infiltrate may be responsible for the functional disturbance. The first report of Gaucher cells in glomeruli concerned a patient who died of sepsis with normal renal function and no proteinuria.

After splenectomy, Gaucher cells often accumulate in organs and tissues other than the reticuloendothelial system. These include internal viscera such as lungs, heart, and kidneys. Morimura et al described a patient with massive infiltration of lungs and kidneys, with resultant pulmonary and renal failure. All but one patient with glomerular disease described in the literature had had a splenectomy; this patient, a child, had membranoproliferative glomerulonephritis without Gaucher cells in glomeruli. Our patient first developed renal manifestations 7 years after removal of the spleen; however, this was a consequence of preeclampsia–induced glomerular endotheliosis from which she recovered completely. It was not until 9 years later that she manifested heavy proteinuria with Gaucher cell–associated glomerular damage. It is tempting to suggest that the replacement therapy was associated with disappearance of the abnormal cells and the vast improvement in clinical manifestations; without a third biopsy, this remains an attractive hypothesis. Morphologic observations on the fate of Gaucher cells consequent to enzyme replacement therapy are limited. A study of two patients by Bove et al suggests an unequal tissue response to therapy; it is likely that Gaucher cells in liver, spleen, and bone marrow, but not lungs or central nervous system, are affected by therapy. Perhaps the kidneys are in the former group of organs. Our experience represents the first report of amelioration of glomerular disease with this form of treatment. It suggests this to be a reasonable therapeutic approach in patients with Gaucher disease with glomerular abnormalities who are not yet receiving enzyme replacement therapy.

REFERENCES

8. Siegal A, Gutman A, Shapiro MS, Griffel B: Renal


