Fabry Disease Associated With Antiglomerular Basement Membrane Disease: Chance or Consequence

To the Editor: Fabry disease is a rare X-linked disease caused by mutations in the gene for alpha-galactosidase resulting in accumulation of glycosphingolipids and dysfunction of cells in many organs, including the kidneys.[1] Antiglomerular basement membrane (Anti–GBM) disease causes glomerulonephritis and pulmonary capillaritis.[2] We report a patient with coexistence of these 2 very rare diseases, which could be by chance alone or pathogenetically linked.

A 29-year-old man developed abdominal pain, flank pain, nausea, and vomiting. He had no hemoptysis.

Laboratory results included creatinine 5.6 mg/dl, albumin 3 g/dl, hematuria, proteinuria 100 mg/dl, normal complement, positive antinuclear antibody, negative antineutrophil cytoplasmic autoantibodies, and positive anti–GBM.

Light microscopy result of a kidney biopsy revealed >80% glomerular cellular crescents and segmental fibrinoid necrosis (Figure 1a). Intact glomerular segments had minimal endocapillary hypercellularity. Podocytes and tubules had marked clear cytoplasmic vacuolization with hematoxylin and eosin and periodic acid–Schiff stains (Figure 1a).

By immunofluorescence microscopy, glomeruli had very strong, diffuse, global, linear GBM staining for

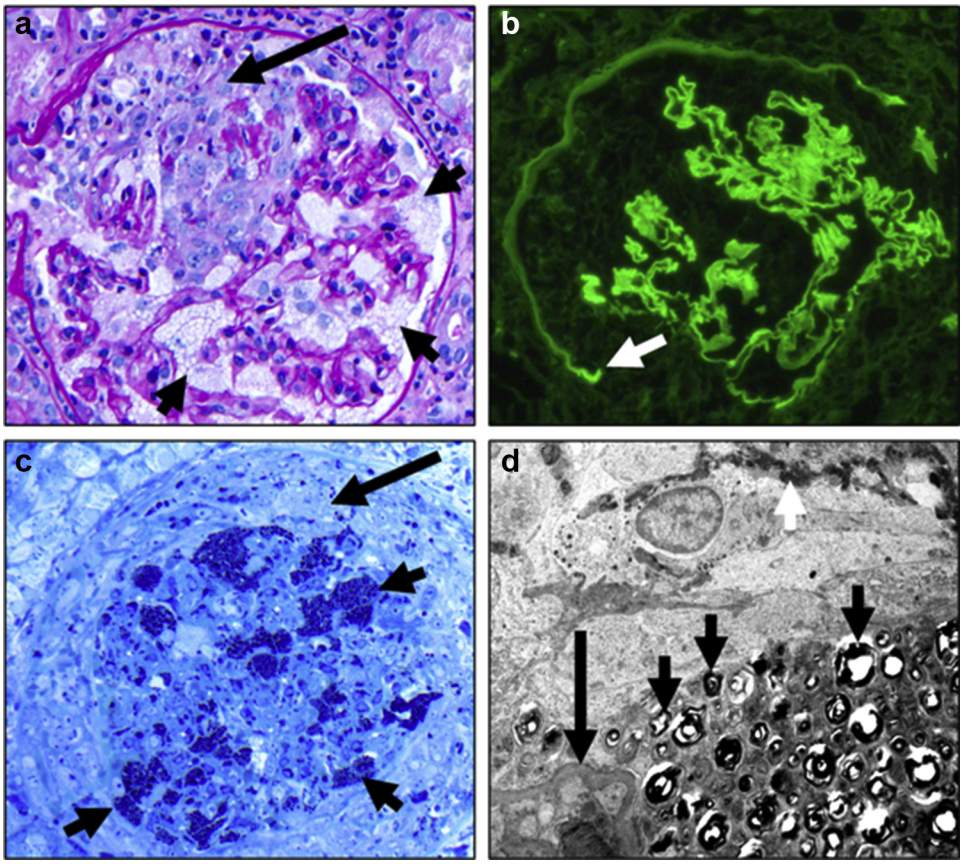

Figure 1. Kidney biopsy results revealed anti–GBM crescentic glomerulonephritis and intracellular inclusions consistent with Fabry disease. (a) Light microscopy image of a glomerulus with extensive clear vacuolation of podocyte cytoplasm (short arrows) and a cellular crescent (long arrow) (PAS stain). (b) Immunofluorescence microscopy image revealing bright linear staining for IgG along the glomerular capillary GBM and Bowman's capsule basement membrane with breaks (arrow). (c) Light microscopy image of a semi-thin plastic section revealing a glomerulus with circumferential cellular crescent (long arrow) and abundant inclusions in podocyte cytoplasm (small arrows) (toluidine blue stain). (d) Electron micrograph revealing numerous, osmiophilic, lamellated inclusions in podocyte cytoplasm (small arrows), GBM at the periphery of the glomerular tuft (long arrow), and a cellular crescent in the upper position of the electron micrograph with electron-dense fibrin tactoids between the cells (white arrow). GBM, glomerular basement membrane; PAS, periodic acid–Schiff.

IgG, kappa light chains, and lambda light chains (Figure 1b), trace to 1+ granular capillary staining for IgM and C3, and no staining for IgA, IgM, or C1q. Glomeruli had focal segmental staining for fibrin, consistent with fibrinoid necrosis and crescent formation.

Result of the plastic sections of the tissue submitted for electron microscopy revealed numerous podocyte toluidine blue positive, oval inclusions (Figure 1c). Electron microscopy result revealed multilamellar lysosomal inclusions consistent with Fabry disease in podocytes, including parietal epithelial cells, tubules, and vessels (Figure 1d).

Fabry disease was confirmed by detecting low blood levels of leukocyte alpha-galactosidase and alpha-galactosidase gene mutations. The rash was identified as multiple small Fabry angiokeratomas. The patient received pulse steroids, oral cyclophosphamide, and plasmapheresis, but these did not regain kidney function.

The association of these 2 very rare diseases could be coincidental or pathogenetically linked. Fabry disease causes podocyte injury. Podocytes produce GBM type IV collagen. Anti–GBM antibodies are directed against conformational changes in type IV collagen that must be exposed to interact with anti–GBM.[3] Hypothetically, in this patient, podocyte injury caused by Fabry disease resulted in synthesis of abnormal type IV collagen with unmasking of pathogenic GBM epitopes.

DISCLOSURE

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PATIENT CONSENT

Consent was received from the patient.

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