

Case Report

Rare Coexistence of Fabry Disease with Class V Membranous Lupus Nephritis

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Fabry disease (FD) is a rare X-linked inherited disorder resulting from deficient α -galactosidase A enzymatic activity due to pathogenic mutations in the α -galactosidase A (GLA) gene [1]. This leads to progressive lysosomal globotriaosylceramide (Gb3) accumulation in a variety of cell types, including vascular endothelial and smooth muscle cells, myocytes and podocytes and other kidney cell types [1].

Microalbuminuria and proteinuria are initial manifestations of renal involvement by FD, with progression to end-stage renal disease in half of the patients [1]. A diagnosis of FD disease is confirmed by deficient α -galactosidase enzymatic activity. Its association with lupus nephritis [2,3] has only been reported in a handful of cases. Here, we report another example of this rare combination.

A 50-year-old man was admitted to hospital for investigation of proteinuria (24-hour urine protein of 5g) after developing swelling in his legs after a flight. His other medical history included obstructive sleep apnoea, cerebral cyst resected at age 22, hypercholesterolaemia, Herpes zoster and minor rectal bleeding secondary to haemorrhoids which had resolved.

Physical examination revealed bilateral lower limb pitting oedema. He was afebrile, and his blood pressure was 150/80mmHg. He had shortness of breath on exertion. During work-up, a CT scan of the chest and abdomen revealed ground glass opacities in the bases of both lungs, associated with perihilar, right inguinal and mediastinal

lymphadenopathy. Renal ultrasound revealed normal sized kidneys and morphology.

Other laboratory values revealed urine protein to creatinine ratio of 500mg/mmol associated with haematuria; serum creatinine, 93 μ mol/L (reference range (RR) 60-110); serum albumin, 34g/L (RR 35-50); estimated glomerular filtration rate, 75ml/min/1.73m² and normal liver function tests.

Further laboratory testing showed mildly elevated double-stranded DNA (6.4IU/mL, RR 0-5), ANA of 1:2560 in a centromere pattern but anti-SCL and other ENA's were negative. Complement levels were normal; C3 being 1.41g/L (RR 0.74-1.57), while C4 was 0.29g/L (RR 0.13-0.41). His serum immunoelectrophoresis (IEPG) showed 2g/L IgM lambda paraprotein and other screening tests for hepatitis B, hepatitis C, urine IEPG and ANCA were negative. His angiotensin-converting enzyme (ACE) levels and coagulation profile were within normal limits.

A renal biopsy was performed. The glomerular features revealed thickened basement membranes, mild segmental mesangial expansion, and occasional vacuoles were seen within podocytes (Figure 1A). The latter feature became more apparent and appreciated following ultrastructural examination.

Immunofluorescence studies (IF) showed coarse granular

capillary loop deposition of IgG (++), IgA (+), IgM (trace, patchy), C3 (++) and C1q (+).

Electron microscopy revealed stage 3-4 membranous glomerulopathy showing numerous subepithelial electron deposits (Figure 2A). Some of these deposits were encased within the thickened glomerular basement membrane, whereas others were resorbed. There was also marked effacement of the foot processes. Other electron-dense deposits and substructures in the other glomerular compartments were not seen. Of interest, large numbers of myeloid bodies or Zebra bodies (Figure 2A) with a lamellated appearance and periodicity of 5nm were seen in the podocytes (Figure 2B). This led to a suspicion of FD. Other storage disorders, which include Gaucher's disease and Niemann-Pick disease, were also possibilities.

To confirm FD, plasma α -galactosidase A activity was measured and detected to be low (0.2nmol/min/mg, normal range, 0.7-3.3), confirming the clinical suspicion. This was supported by Sanger sequencing detection of the p. N215S mutation in the GLA gene, typically associated with non-classical FD1 and the most common mutation in the Western world. This mutation results from an A-to-G transition at codon 215 in exon 5 of GLA (NM_00169.2:c.664A>G), with subsequent substitution of a glycosylated asparagine by a serine. He did not have other biochemical tests to exclude other storage disorders.

Testing for anti M-type phospholipase A2 receptor antibody (PLA2R1), a marker for primary idiopathic membranous glomerulonephritis [4] was negative. Although his clinical presentation was atypical, the diagnosis of lupus nephritis was based

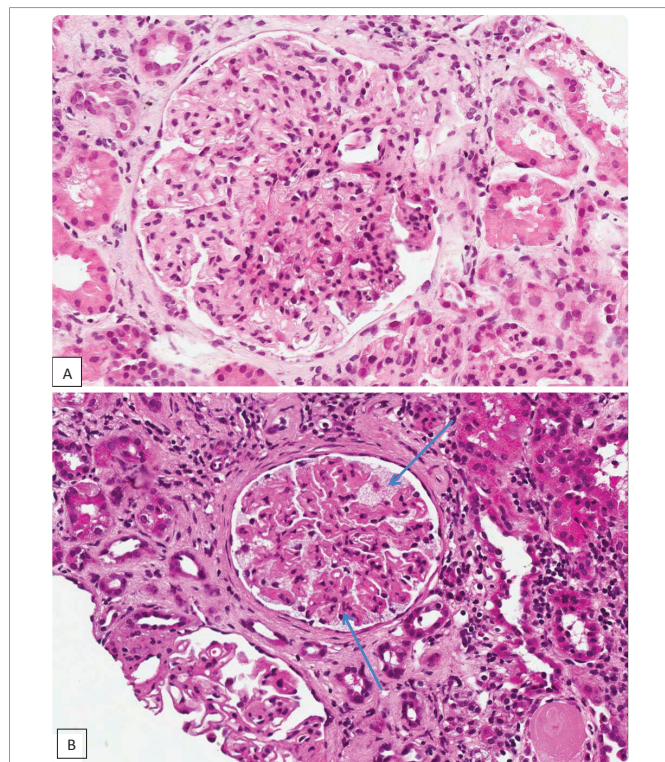


Figure 1: (A) First renal biopsy, H&E x400; (B) Second renal biopsy, H&E x200 with glomeruli showing thickened glomerular basement membranes and vacuoles within podocytes (arrows).

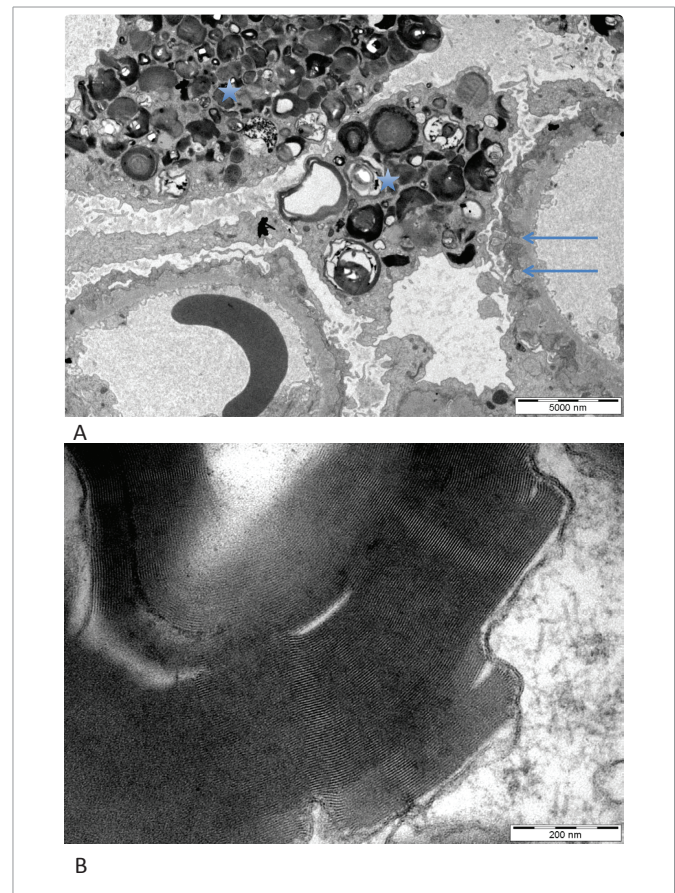


Figure 2: (A) Electron microscopy showing subepithelial electron-dense deposits (arrows) and myeloid bodies (stars) (x 5200; scale bar, 5000nm); (B) Lamellated appearance of myeloid bodies (x 14000; scale bar, 200nm).

on the presence of double-stranded DNA, abnormal ANA pattern and his immunofluorescence studies showing full-house deposition of immunoglobulins including C1q. The final diagnosis was concurrent Fabry disease and class V membranous lupus nephritis (MLN).

He was commenced on enzyme replacement therapy with agalsidase alpha for FD. He was also placed on prednisone and Myfortic for co-existing class V membranous lupus nephritis. However, the patient's renal function continued to deteriorate rapidly, out of keeping with the diagnosis of non-classical FD. A second renal biopsy, ten months following his first renal biopsy, showed acute interstitial nephritis, in addition to MLN and Fabry disease. This led to the withdrawal of enzyme replacement therapy. The glomerular features, which featured thickened glomerular basement membranes and vacuoles within the podocytes, were more pronounced in the second renal biopsy (Figure 1B).

The patient later suffered an episode of pericarditis, one of many presentations of systemic lupus, validating support for a diagnosis of MLN. He remained in partial clinical remission with stable kidney function. His complements and double-stranded DNA normalised following treatment with prednisone and Myfortic, although he had ongoing proteinuria.

A follow-up echocardiogram revealed left ventricular hypertrophy, indicating cardiac involvement by Fabry disease.

Myeloid bodies were also detected on ultrastructural examination on lung tissue biopsy, confirming pulmonary involvement. There was a consideration whether enzyme replacement therapy should be recommenced. However, the patient was reluctant, given the possibility that his deterioration in renal function was related to enzyme replacement therapy.

The case report highlights the importance of electron microscopy in unravelling a suspected diagnosis of FD when myeloid bodies are seen ultrastructurally. Myeloid bodies are single, membrane-bound, lysosomal-like bodies thought to contain hydrate lipid residues [5]. In FD and other storage disorders, the absence of a specific lysosomal hydrolase is believed to lead to accumulation of undigested material in the lysosome. Myeloid bodies or similar bodies are the product of metabolic defect or toxic cell damage. Oxidative damage by the related metabolite globotriaosylsphingosine has also been documented [6].

However, myeloid bodies may be associated with other glomerulopathies not linked to FD [7,8] as well as drug therapy, which include gemcitabine [7], amiodarone [9], and chloroquine [10]. Therefore, measurement of plasma α -galactosidase A activity is essential in establishing a diagnosis of FD.

Measurement of anti M-type phospholipase A2 receptor antibody (PLA2R1) may establish whether membranous glomerulonephritis is a primary or secondary process [8]. In our case, the serum anti-PLA2R1 antibodies were not raised, and lupus serology was positive, indicating concurrent secondary membranous glomerulonephritis due to lupus.

It is possible that their co-existence may be coincidental. Genetic links between the two disease processes have not been established. One study, however, suggests that Gb3 is immunogenic and provides a continuous stimulus, potentially by changing the nature of lymphocyte cell membranes, thereby creating an environment able to sustain autoimmune responses [11]. Also, patients with lupus are characterized by an altered composition of lymphocyte cell membrane lipids, including Gb3 that can increase their activation [12].

This may explain the mechanism for this rare association in which defects in lipid biosynthesis, such as seen in FD, could contribute to the development of autoimmunity, such as systemic lupus. That may explain their similarities in the organs involved by these two multisystem disorders. Countering this hypothesis is the fact that we would expect to see more than a handful of cases with the

combined pathology if we consider all the patients diagnosed with FD worldwide. Further studies are however required for clarification.

Conflicts of Interest

The authors state that there are no conflicts of interest to disclose.

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