**EXCEPTIONAL CASE**

Relapsing minimal change disease superimposed on late-onset p.N215S Fabry nephropathy

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**ABSTRACT**

We present the case of a 76-year-old man with late-onset Fabry disease caused by the p.N215S missense mutation, with Fabry cardiomyopathy and nephropathy. In this case, the diagnosis of Fabry disease was incidental and followed minimal change disease (MCD) onset, with nephrotic syndrome and acute kidney injury requiring renal replacement therapy. Fabry nephropathy associated with the p.N215S mutation is becoming increasingly recognized among older patients. The importance of electron microscopy is herein highlighted and histological features common to Fabry nephropathy and MCD are discussed, along with the challenges associated with the diagnosis and clinical management.

**Keywords:** acute kidney injury, Fabry disease, Fabry nephropathy, genotype-phenotype correlation, minimal change disease, nephrotic syndrome, superimposed glomerulopathies

**INTRODUCTION**

Fabry disease is an X-linked lysosomal storage disease caused by a GLA gene mutation, leading to deficient activity of the α-galactosidase A (α-Gal A) enzyme, resulting in progressive lysosomal glycosphingolipid accumulation. The p.N215S mutation is one of the most common missense mutations causing late-onset Fabry disease and is typically associated with hypertrophic cardiomyopathy. More recently, this mutation has also been associated with Fabry nephropathy, with uncertain clinical outcomes. Herein we present the case of an older man with typical p.N215S late-onset Fabry disease, nephropathy and superimposed minimal change disease (MCD).

**CASE REPORT**

The patient was known for idiopathic hypertrophic cardiomyopathy and chronic kidney disease (CKD) not otherwise investigated since the age of 64 years. At the age of 65 years he was admitted for acute kidney injury (AKI) requiring renal replacement therapy and nephrotic syndrome (serum creatinine 7.6 mg/dL, proteinuria 24 g/day). Kidney biopsy was performed and light microscopy revealed mild mesangial hypercellularity but was otherwise unremarkable. Unexpectedly, electron microscopy showed tubular epithelial intralysosomal lamellar and concentric inclusions (myelin bodies); no glomeruli were available for analysis. Leukocyte α-Gal A activity was impaired (15%...
of the lower limit of normal). Genetic analysis revealed the missense mutation p.N215S and late-onset Fabry disease was diagnosed.

The patient was empirically treated with oral prednisone 1 mg/kg/day for 1 month with subsequent clinical remission [Figure 1C; proteinuria 0.17 g/day, estimated glomerular filtration rate (eGFR) 26 mL/min/1.73 m²]. Enzyme replacement therapy (ERT) with agalsidase alfa (0.2 mg/kg every other week) was started upon proteinuria remission. Four years later, cardiomyopathy progression required positioning of an implantable cardioverter defibrillator and ERT switch to agalsidase beta (1 mg/kg every other week). He has been clinically stable for >4 years.

At the age of 75 years, the patient was admitted to our hospital for nephrotic syndrome relapse with AKI. Repeat kidney biopsy was performed. Light microscopy showed mild, diffuse mesangial hypercellularity, global diffuse podocyte hypertrophy and tubulointerstitial atrophy with intratubular hyaline casts. Small vessels showed intima-media hyperplasia and focal hyalinosis of the arteriolar wall. Immunofluorescence was negative for all antisera. Electron microscopy found complete, diffuse podocyte effacement (Figure 1A) and scattered podocyte myelin bodies (Figure 1B). Screening for immune-mediated glomerulopathies was negative.

Based on biopsy findings and clinical history, relapsing MCD superimposed on Fabry nephropathy was diagnosed. The patient was treated with three 500 mg intravenous methylprednisolone boluses (one every 3 days), followed by oral prednisone 0.5 mg/kg/day for 2 months, followed by tapering. Clinical
remission was achieved within 4 months and prednisone was discontinued after 6 months. At remission, proteinuria was 0.6 g/day and eGFR was 27 mL/min/1.73 m².

At the age of 76 years, admission following a disease relapse was necessary. Steroid therapy was started following the same protocol. AKI required renal replacement therapy and was discontinued after 10 days. At hospital discharge, partial remission was observed with further improvement 2 months later. Prednisone was discontinued after 6 months, achieving a proteinuria of 0.6 g/day and an eGFR of 38 mL/min/1.73 m².

DISCUSSION

Few reports of biopsy-documented Fabry nephropathy associated with the p.N215S mutation are available to date. Kidney glycosphingolipid deposits have been previously shown in a patient with the p. N215S mutation [1]. From international registry data, Germain et al. [2] reported that 17% of p.N215S patients had CKD upon their first assessment. However, histology was unavailable.

Late-onset p.N215S mutation with relapsing MCD superimposed on Fabry nephropathy is a rare occurrence and its management presents some challenges. In this case, although typical hypertrophic cardiomyopathy had been known since the age of 64 years, Fabry disease was incidentally diagnosed 1 year later due to MCD onset, thanks to electron microscopy. Fabry nephropathy typically presents with isolated, non-nephrotic proteinuria in the third and fourth decade in males with classical Fabry disease and in later decades in late-onset phenotypes. Typical electron microscopy findings include intralysosomal myelin bodies in glomerular podocytes and tubular epithelial cells [3]; podocyte effacement is common to both Fabry nephropathy and MCD, and diagnostic challenges arise with histology alone. Steroid response, relapsing nephrotic syndrome with AKI, the lack of specific light microscopy findings and podocyte effacement on electron microscopy allowed the MCD diagnosis.

AKI affects 20–35% of adult MCD cases and is associated with older age, massive proteinuria, severe hypoalbuminemia and hypertensive vascular damage on light microscopy [4]. Relapses have been reported in up to 80% of adult MCD patients [5]. Long-term prognosis in adult MCD is benign; progression to end-stage renal disease is uncommon and is associated with underlying focal segmental glomerulosclerosis [5]. In this case, Fabry nephropathy had a benign course, likely due to a late-onset phenotype and ERT.

Our patient currently remains free of renal replacement therapy. This case highlights the importance of kidney biopsy and electron microscopy in non-classical Fabry disease and the challenges associated with superimposed immune glomerulopathies.

PATIENT CONSENT

The patient gave informed consent to publish this case.

CONFLICT OF INTEREST STATEMENT

F.P. received lecture fees and travel funding from Sanofi Genzyme, Takeda, Amicus Therapeutics and Chiesi Farmaceutici. The other authors have nothing to disclose. The results presented in this article have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

Data will be shared on reasonable request to the corresponding author with the patient’s permission.

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