Case Report

Coexistence of Fabry Disease and Membranous Nephropathy: A Case Report

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Fabry disease (FD) is a rare X-linked genetic disease that can coexist with multiple glomerulopathies. We report a 32-year-old female patient of FD coexisting with stage II membranous nephropathy (MN), who presented with proteinuria, normal renal function, and hypo-hidrosis as the only symptom. The renal biopsy manifested a subepithelial immunocomplex deposit in the glomeruli along with basement membrane thickening on light microscopy. Electron microscopy revealed myeloid bodies in some podocytes, which suggested the patient possibly coexistence with Fabry disease. The low activity of α-galactosidase A and one pathogenic heterozygous mutation (c.335G > Ap.Arg112His) in the α-galactosidase A gene confirmed the diagnosis of Fabry disease. This patient's son had the same gene mutation as his mother but without any symptoms at the time. Treatment with ramipril turned urine protein negative. The proteinuria had reoccurred, as shown by the presence of foamy urine, a protein to creatinine ratio of 1.54 g/g, and a blood albumin level of 34.4g/L. The patient was being treated with Allisartan Isoproxil. However, at the time, the urine protein did not turn negative.

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INTRODUCTION

Fabry disease (FD) is a rare X-linked metabolic disease caused by a deficiency of lysosomal α-galactosidase A (α-Gal A), globotriaosylceramide and other glycosphingolipids accumulate in blood vessels, leading to multi-system dysfunction including renal, cardiac, cerebrovascular, and skin disorders.[1-2] FD could infrequently coexist with various glomerular diseases, including IgA nephropathy,[3] focal segmental glomerulosclerosis,[4] lupus nephritis.[5] There have been two reports of male FD and membranous nephropathy (MN) coexistence.[6-7] We described the first case of a female heterozygous for FD coexisting with stage II MN, who was asymptomatic and had complete remission without immunosuppression.

CASE PRESENTATION

The 32-year-old female patient went to The First Affiliated Hospital of USTC in February 2019 due to proteinuria that persisted for more than 10 months and was solely associated with hypohidrosis, even less sweat in hot summer, without angiokeratosis, telangiectasia, acroparesthesia, blurred vision, chest tightness, or gastrointestinal symptoms. She denied a family history of hypertension or renal disease. Physical examination revealed a blood pressure of 123/97mmHg, heart rate of 85 beats/ minute with no pathological murmur on cardiac examination. Tests results indicated a 24-hour proteinuria of 3256 mg/d, blood albumin of 23.8g/L, serum creatinine of 29 umol/L, and hepatitis C, hepatitis B, syphilis, and AIDS were all negative. Echocardiography showed no abnormalities. A

kidney biopsy was performed. There was no spherical or segmental sclerosis in 34 glomeruli on light microscopy. The glomeruli exhibited partial podocyte vacuolar degeneration, glomerular basement membranes thickening, and subepithelial immunocomplex deposition. Immunofluorescent revealed IgG (+++), IgG4 (+++), C3 (++), IgM (+) and PLA2R (++) deposition along the capillary loops (Figure 1), that resulted in the diagnosis of MN. Electron microscopy revealed myeloid and zebra bodies in some podocytes (Figure 2). The patient was diagnosed with MN, possibly coexisting with FD. However, due to financial constraints, the patient declined to perform genetic testing. Ramipril 5mg/day was initiated, and proteinuria achieved complete remission in July 2019, the complete remission lasted until March 2020. After that, the patient failed to return for a follow-up appointment. In June 2022, the patient presented again with proteinuria of 2266 mg/24h, PCR 1.54g/g, creatinine 41umol/L, serum albumin of 34.4g/l, serum PLA2R < 20 RU/ml (reference range < 20 RU/ml). Figure 3 and Figure 4 show the changes in laboratory indicators throughout the treatment process. This time, the patient underwent FD-related tests, which revealed α-Gal A activity of 2.33umol/L/h (reference range 2.40-17.65umol/L/H) and Lyso-GL-3 of less than 0.55ng/ml (reference range < 1.11ng/ml). Gene analysis indicated one pathogenic heterozygosity

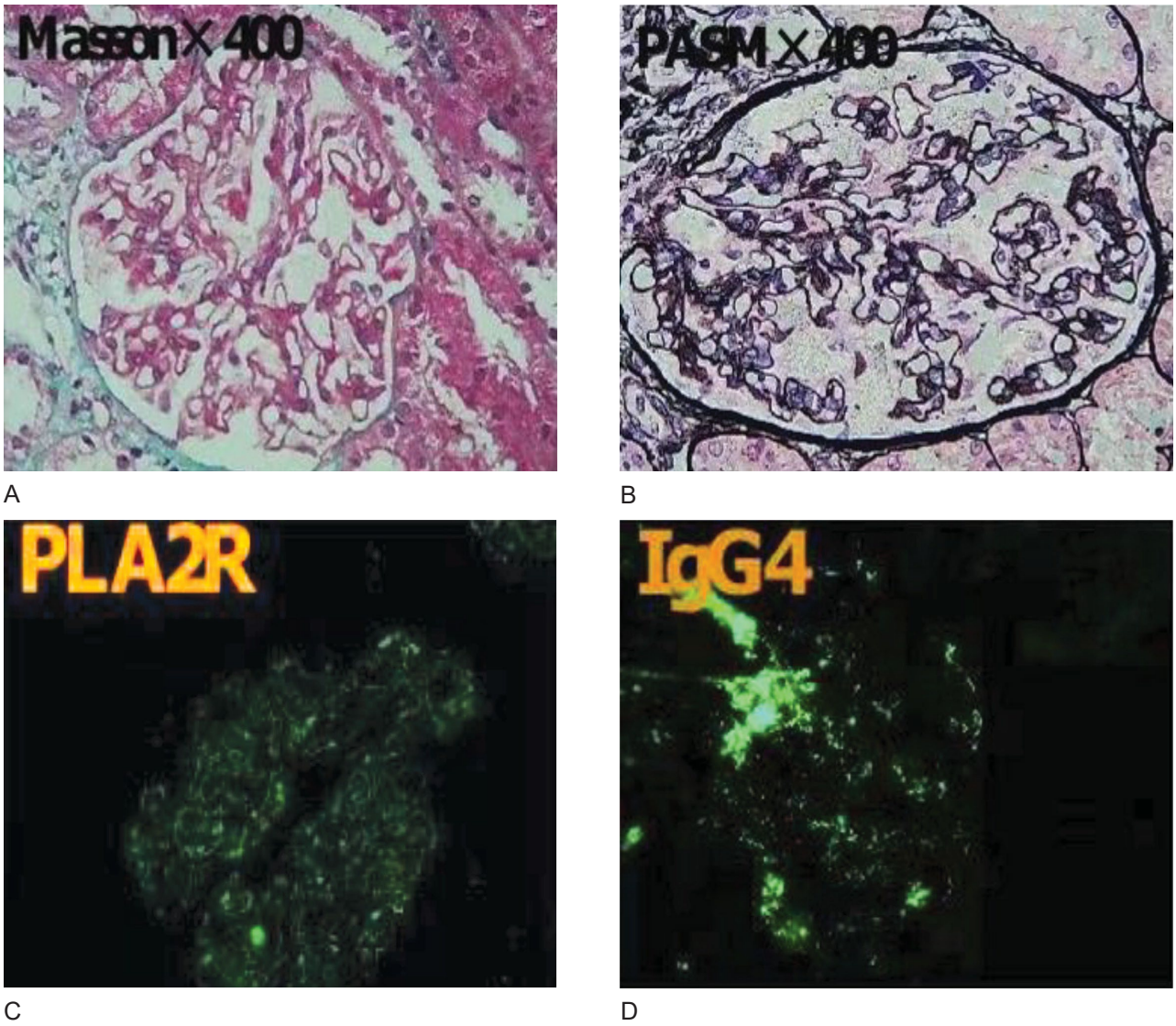
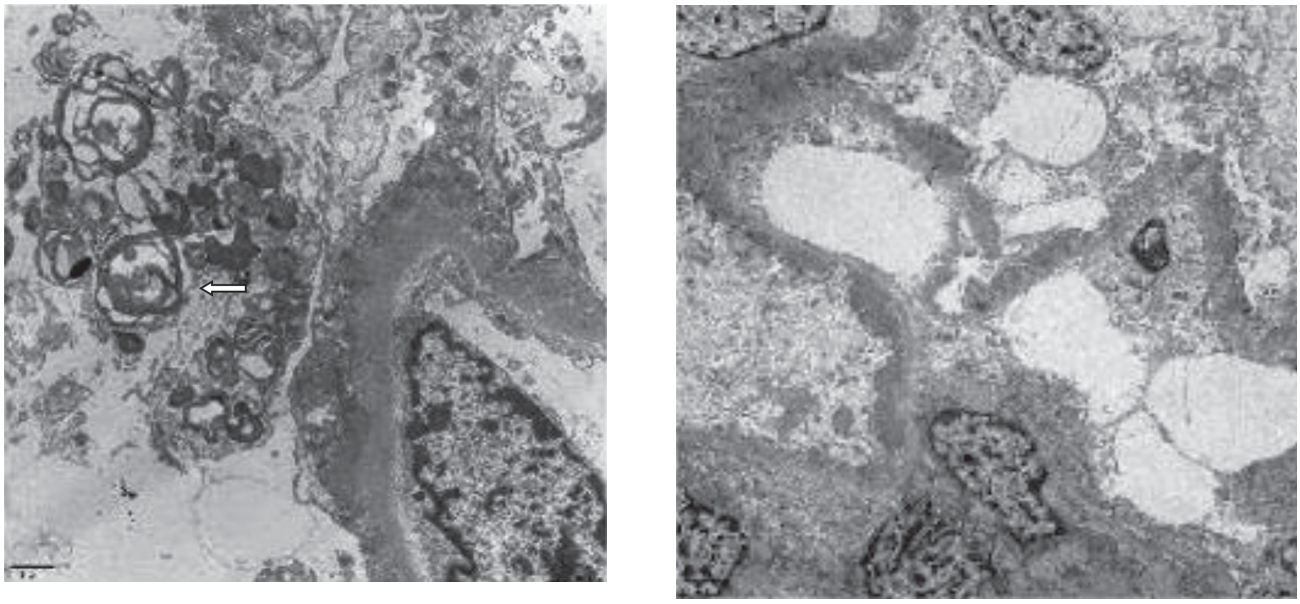


Figure 1. Immunofluorescence showed PLA2R and IgG4 deposition in granular form; Light microscope: mild hyperplasia of glomerular mesangial and matrix, thickened basement membrane, and significant vacuolar degeneration of podocytes.



A B

Figure 2. Podocyte foot process diffuse fusion, individual podocytes appear as foam, secondary lysosomes were increased with myeloid bodies and particular zebra body sample.

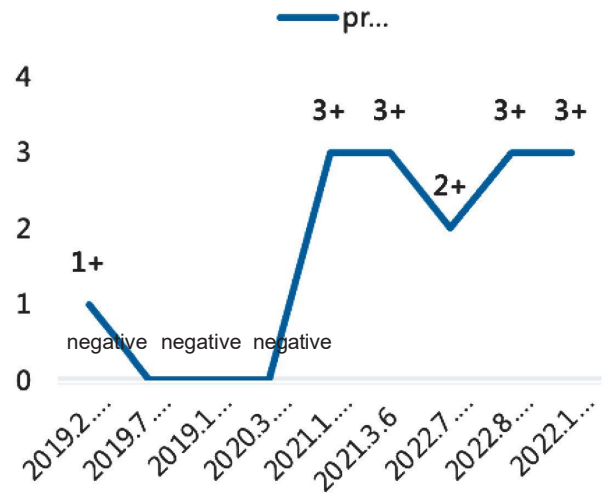


Figure 3. The dynamic changes of urinary proteinuria

variant in the α-Gal A gene (c.335G > Ap. Arg112His), which is considered to be Fabry's pathogenic gene.[8] The patient's 7-year-old son had the same gene mutation as his mother, α-Gal A activity was 0.44umol/L/h, Lyso-GL-3 < 2.22ng/ml, and showed no symptoms or discomforts. The patient was treated with Allisartan 240mg/day. We are still monitoring the patient and her son condition closely.

DISCUSSION

There are two types of FD: classic and late- onset. Typical patients are usually male, while female patients are often heterozygous and may have regular α-Gal A activity.[9] The heart and the kidneys are the main organs involved in FD.[10]

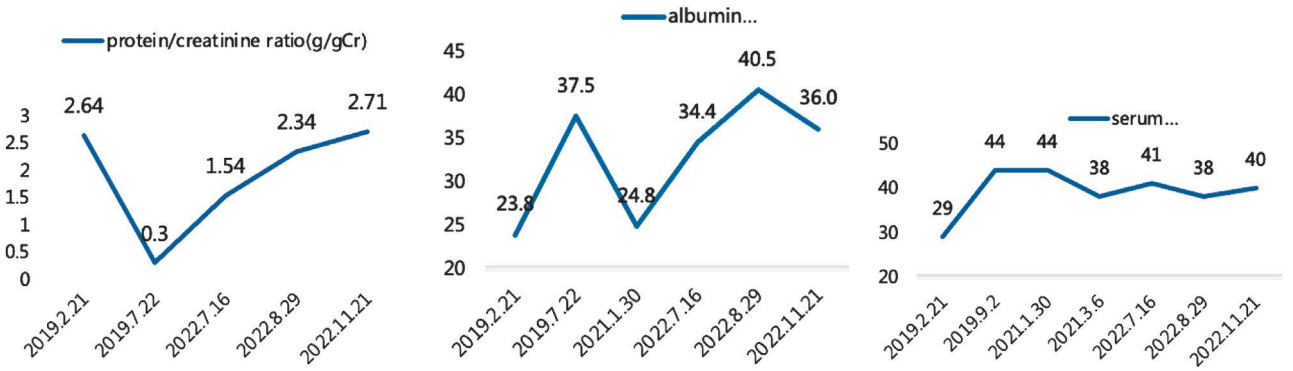


Figure 4. The dynamic changes of urinary protein/ creatinine ratio, blood albumin and serum creatinine.

Diagnostic methods include measurement of α-Gal A enzyme activity.[11] genetic testing,[11] biomarker analysis (GL-3,[12-13] and Lyso-GL-3[14] levels), and histopathology examination.[15-16] Among all, genetic testing is the gold standard for the diagnosis.[15] The accumulation of GL-3 in podocytes of kidneys leads to renal damage and proteinuria, the most common form of renal injury in FD.[17] The primary clinical manifestation of this patient was proteinuria, so we should closely monitor the changes in proteinuria. In March 2022, the reappearance of proteinuria and PLA2R < 20RU/ml indicated a low likelihood of MN recurrence, but also a high probability of progression of Fabry. MN recurrence and FN progression can both be treated with angiotensin-converting enzyme inhibitors or angiotensin receptor inhibitor.[18-20]

Identical to the reports of Ying Liu[6] and Wenyan Zhou, the three patients in their study had no or few family history of extrarenal manifestations and were not treated with ERT (enzyme replacement therapy) due to financial reasons. Our main difference was that we reported the only late-onset female patient who achieved complete remission without immunosuppressive. The gene mutation was the same as Ying Liu patient but differs from Wenyan Zhou (Table). This case highlights the importance of kidney biopsy; electron microscopy plays a critical role in the diagnosis of FD. Light microscopy, immunofluorescence and electron microscopy are essential in diagnosing renal diseases. But renal biopsy cannot completely diagnose all diseases, so it is necessary to use genetic testing and other techniques.[21-22] Therefore, a thorough understanding of kidney-related disease diagnosis and therapy is required.

Table .Comparisonwith twoother casesofFD coexistwithMN

Case	Sex	Age	Mutation gene	Therapy	Follow-up time	Skin rashes	Arthralgia	Blurred vision	Chest tightness	Hypohidrosis	Gastrointestina symptoms	Neuralgia	Family History
Yan Jin	F	32	c.335G>ApArg112His	ARB	3 years	NO	NO	No	No	Yes	No	No	the patient' s son
Ying Liu	M	21	c.335G>Ap.Arg112Hi	ARB	2 years	NO	NO	No	No	No	No	No	unstated
Wy Zhou	M	30	GLA-E07.1286_*7 del	ARB	1 year	NO	NO	No	No	No	No	No	unstated

ETHICS STATEMENT

The protocol and consent processes were approved by the Ethics Committee of the First Affiliated Hospital of USTC (ID: 2023-RE-011). Written informed consent was obtained from the patient.

CONSENT FOR PUBLICATION

NA

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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