

Fabry disease and immunoglobulin A nephropathy presenting with Alport syndrome-like findings

A case report

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Abstract

Rationale: Fabry's disease is an X-linked inherited syndrome. Herein, we presented an unusual case of Fabry disease coexisting with immunoglobulin A nephropathy (IgAN) presenting with Alport syndrome-like pathological findings.

Patient concerns: We report a 30-year-old male who presented with proteinuria and elevated serum creatinine and for whom the initial pathologic diagnosis supported Alport syndrome.

Diagnoses: A diagnosis of Fabry disease with immunoglobulin A nephropathy (IgAN) was finally made after further examination.

Interventions: After the initial diagnosis the patient was treated with herbal medications and mecobalamin.

Outcomes: The patient was discharged 1 week later. He was maintained on these treatments and received regular follow-up in our hospital.

Lessons subsections as per style: FD coexisting with IgAN is rare and may have nonspecific clinical presentations. Laboratory examination and genetic diagnosis is needed for confirmation. Timely diagnosis and reproductive intervention is needed for therapy.

Abbreviations: FD = Fabry disease, Gb3 = glycosphingolipid globotriaosylcerami, GLA = α -galactosidase-A, IgAN = immunoglobulin A nephropathy.

Keywords: Alport syndrome, Fabry disease, immunoglobulin A nephropathy

1. Introduction

Fabry's disease is an X-linked lysosomal storage disorder caused by abnormalities in the GLA gene, which leads to a deficiency in α -galactosidase A. The consequent abnormal accumulation of glycosphingolipids results in several clinical signs and symptoms and substantial morbidity and mortality.^[1] IgA nephropathy, first described by Berger and Hinglais in 1968, is now one of the most common forms of primary glomerulonephritis.^[2] Case of IgA nephropathy with concomitant Fabry's disease is rare. Only 27

patients were reported in PubMed who are often misdiagnosed on admission.^[2–15] The association between Fabry disease and IgAN has been previously anecdotally reported, but no systematic study was undertaken. Besides, none of pathological findings of these 27 patients like Alport syndrome. Here, we report on a case of Fabry disease and immunoglobulin A nephropathy presenting with Alport syndrome-like findings. We review the literature and analyzed clinical characteristics, pathologic findings, common pathophysiology between Fabry disease and IgAN, histopathologic characteristics and differences in inheritance patterns of Fabry disease and Alport syndrome for the purpose of providing clinical insight, and facilitating more accurate clinical diagnosis.

2. Case description

A 30-year-old male was admitted to our hospital due to 1 month of fatigue without medical attention and edema occurring from 3 days previously. The edema was unprovoked, and he first visited our hospital for evaluation. Serum tests in the out-patient clinic showed a creatinine level of 150 μ mol/L, and a random urinalysis found 3+ protein. He denied any family history of renal dysfunction, and physical examination showed blood pressure of 129/76 mmHg, heart rate of 80 beats per min, and normal cardiopulmonary and neurologic findings without costovertebral knocking tenderness. Mild leg edema was noted. A repeat urinalysis on admission showed still 3+ protein, and the 24-hour urine protein level was 2.73 g. Serum biochemistry showed a creatinine concentration of 136.1 μ mol/L, uric acid concentration of 450 μ mol/L, albumin

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Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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concentration of 31.6 g/L, and total protein concentration of 52.6 g/L. Serum electrophoresis revealed 55.7% albumin, 4.1% α 1 globulin, 12.3% α 2 globulin, and 18.3% γ globulin, while a rheumatologic panel did not have positive findings. Chest X-ray was normal, and electrocardiography showed sinus bradycardia only. Renal sonography found increased bilateral kidney echogenicity, and abdominal sonography revealed hemangioma only.

We then performed renal biopsy. Thirteen glomeruli were obtained, of which 10 (76%) had glomerular sclerosis, and 2 out of the remaining 3 glomeruli exhibited segmental endothelial, mesangial, and podocyte proliferation, accompanied by variable degrees of basement membrane thickening. Only one glomerulus had an intact capillary tuft. Prominent tubular vacuolization with foamy changes and scattered foci of mild tubular atrophy were also found. Multiple areas of foamy cells with lymphocyte and macrophage infiltration and mild fibrosis were noted in the interstitial space, accompanied by arteriolar endothelial swelling with mild intimal edema and hyalinized wall changes (Fig. 1A). Immunofluorescent staining of two glomeruli showed trace IgG, 1+ IgM, 2+ IgA, 1+ C3, and trace C1q in mesangial with negative C4 and complement F staining.

His initial pathologic diagnosis was diffuse proliferative and sclerosing IgAN, but further staining for type IV collagen was recommended to exclude Alport syndrome (Fig. 1B). Indirect immunofluorescent staining showed 1–2+ linear staining of type

IV collagen α 2 chain in the glomerular basement membrane and 2+ linear staining in Bowman's capsule, 2–3+ linear staining of type IV collagen α 5 chain in glomerular basement membrane, 2+ linear staining in Bowman's capsule, and 2+ linear staining in tubular basement membrane. Indirect immunofluorescent staining of skin showed 2+ linear staining of type IV collagen α 2 and α 5 chains. We also performed immunofluorescent staining for the type IV collagen α 2 and α 5 chains in the skin from patient's mother, and the results were 2+ for both.

Electron microscopy showed mild segmental proliferation of mesangial cells and mesangium, with small blots of electron-dense deposits in mesangium. Basement membrane segmental thickening accompanied by massive sphingolipid accumulation in podocytes (Fig. 1C) and minor sphingolipid accumulation in mesangial cells (Fig. 1D) was also noted. Diffuse foot process fusion with increased lysozyme body in tubular cells was identified, without interstitial changes. A final diagnosis of Fabry disease with IgAN was made. Ophthalmologic examination of this patient showed no fundic abnormality, but he refused audiologic examination.

We prescribed herbal medications (Jin-Shuei-Bou, Hai-Sheng-Kun-Shi capsules, and Niao-Du-Ching granules) and mecobalamin for treatment, and the patient was discharged 1 week later. He was maintained on these treatments and received regular follow-up in our hospital. At the first follow-up visit, 6 months

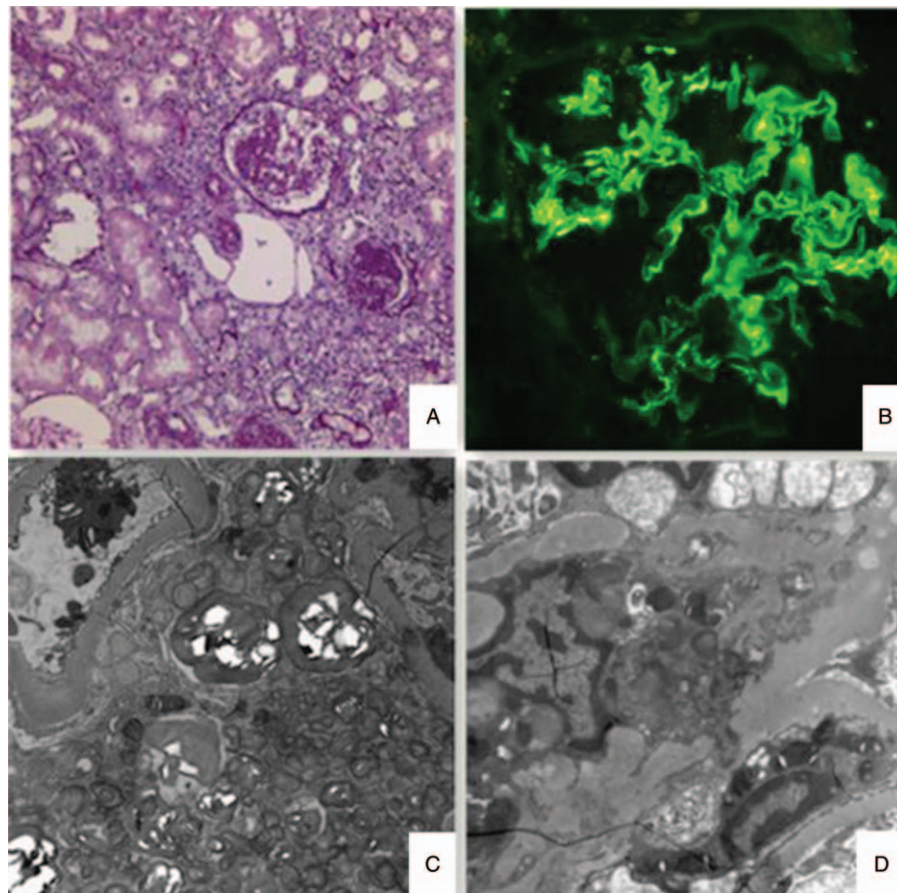


Figure 1. (A) Under light microscopy, multiple foci of foamy cells were found (periodic acid Schiff stain, 200 \times). (B) Immunofluorescent staining showed IgA staining over mesangial areas (400 \times). (C, D) Under electron microscopy, extensive sphingolipid body deposition in podocytes (C) and a small amount in mesangial cells (D) were noted.

after the end of therapy, the patient showed a remission of the disease, the routine laboratory tests were normal.

3. Discussion

Fabry disease (FD), or Anderson-Fabry disease, α -galactosidase-A deficiency,^[16] is a rare X-linked lysosomal deposition disorder, first described by Fabry and Anderson in 1898. Deficiency in α -galactosidase-A (GLA) leads to accumulation of the neutral glycosphingolipid globotriaosylceramide (Gb3) in multiple organs. FD is the second most common metabolic storage disease after Gaucher disease^[17] and includes three pathologic types: classic, renal-, and cardiac-variant. The mutated gene is located in Xq22.1, is 12 kilobases long, and contains 7 exon regions, all of which have been reported to contain hot spots of mutation. The main site of mutation in the GLA gene predominantly involves the enzymatic active site, causing a direct influence on enzymatic activity; alternatively, mutation can involve regions distant from the active sites, exerting an indirect influence on the stability, folding, or transport of the product enzyme.^[18]

FD mostly affects adolescents and is more likely to be symptomatic in males with multisystem manifestations. In affected females, the time of symptom onset is later, with less disease severity. FD frequently manifests with proteinuria and extrarenal symptom/signs including cutaneous angiokeratoma, anhidrosis, peripheral neuropathy, cerebrovascular accident, cardiovascular damages, ophthalmologic lesions such as retinal, corneal, and conjunctiva abnormalities.^[19] Affected patients have decreased serum, leukocyte, and fibroblast α -Gal A activity with increased serum and urine Gb3 level,^[20] but 30% of females with heterozygosity have been found to have normal serum GLA activity. Female FD patients have normal or mildly increased lysosomal Gb3 levels. Pathologically, diffuse podocyte vacuolization is prominent,^[21] while immunofluorescent staining often yields negative or nonspecific findings, such as irregular deposition of IgM, IgA, and C3. Under electron microscopy, sphingolipid deposition, or zebra bodies of 1–3 μ m size in podocytes or other renal cells, is a characteristic presentation. The deposition, glycosphingolipid inclusion body, appears like laminations with light-dark alternations or concentric onion ring-like shapes.^[22] Although renal injuries caused by other lysosomal storage diseases or chloroquine or aminoglycoside exposure may have similar presentations, sphingolipid depositions in these diseases are less likely to be found, are not found in podocytes, and do not contain ultrastructural findings such as laminations with light-dark alternations.^[23] In addition, osmiophilic inclusion bodies in these diseases are smaller (0.5–1 μ m) and have a shorter distance between the light-dark stripes.^[24]

Treatment modalities for FD include enzyme replacement therapy (ERT), pharmacologic chaperons, hemodialysis, and renal transplantation. If intractable pain, progressive renal, cardiac damage, cerebrovascular lesions, or severe gastrointestinal symptoms occur, ERT will be indicated. Common adverse effects associated with ERT include infusion reactions such as headache, abdominal pain, or shock; fever; nausea; and the appearance of antidrug antibodies. ERT is contraindicated in pregnant or lactating women and in those with severe complications unlikely to benefit from receiving ERT. In 2018, Galafold (migalastat), a pharmacologic chaperon, became the first oral medication to be approved; this medication exhibits a high affinity for the mutated site of α -Gal A and is capable of

selectively binding the mutated enzyme in a reversible fashion. Binding between the chaperon and mutated α -Gal A can restore the normal enzymatic folding within the endoplasmic reticulum, leading to effective clearance of sphingolipid deposition.^[25] Apart from a pharmacologic chaperon, Pegunigalsidase α and I lucerastat can also be promising agents in the future, although they are still in development.^[26] According to a 1-year Phase 1/2 clinical trial, Pegunigalsidase α , a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics.^[27] It is a candidate drug produced by polyethylene glycol-linked recombinant α -galactosidase-A, administered as an infusion directly into the bloodstream. It aims to replenish levels of this enzyme in people with Fabry disease. α -galactosidase-A chaperone is indicated for a limited number of patients with specific “amenable” mutations, While I lucerastat is an orally bioavailable inhibitor of glucosylceramide synthase (GCS) that is in late stage clinical development for Fabry disease.^[28]

On the other hand, IgAN has a complicated clinical picture, with presentations varying from pure hematuria or proteinuria to nephrotic syndrome or renal insufficiency, without typical symptoms. Accurate diagnosis relies on renal biopsy, with findings including IgA-predominant granular or mass-like depositions in the mesangial area. Under light microscopy, mesangial cell proliferation with matrix expansion can be found, accompanied by segmental or global sclerosis with crescent formation. Under electron microscopy, electron dense deposits in mesangial areas are a typical finding, which could be found in our patient.

It is still unclear whether FD and IgAN share a common pathophysiology. Maixnerova et al proposed that the coexistence of FD and IgAN could be coincidental, since the incidence of IgAN is high.^[9] However, Shimohata et al and Whybra et al found that Gb3 was structurally similar to a nephritogenic glycopeptide and might induce progressive glomerulonephritis.^[10,12] This is supported by the disappearance of mesangial IgA after ERT in certain FD patients. Martinez et al also found that FD patients had a high level of autoantibodies, deposition of which can induce autoimmune reactions, including immune-mediated glomerulonephritis. In addition, FD has been reported to coexist with rheumatoid arthritis and lupus erythematosus, but the mechanism behind this phenomenon is still unclear.^[29] We reviewed the literature pertaining to FD coexisting with IgAN within the PUBMED and other Chinese databases, and a total of 25 cases (2 excluded due to language issues^[30,31]) were found (Table 1). More than 80% of cases were from Asian countries (China and Japan), with average ages of 34.5 years for males and 30.3 years for females. The clinical presentation in these cases was predominantly proteinuria and hematuria, and the main stay of treatment was ERT (36%) with or without angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, ERT is not available in China, and thus, we did not administer ERT to our patient. Finally, a previous report suggested that FD coexisting with IgAN mainly occurs in females, especially those with end-stage renal disease,^[2] but our literature review did not support this claim.

Our index patient had an indolent clinical course, with initial presentations of proteinuria and increased creatinine, but the pathologic findings under light microscopy and immunofluorescent staining were atypical initially, leading to a false diagnosis of Alport syndrome after biopsy. In contrast to the inheritance pattern of FD, that of Alport syndrome is more complicated.

Table 1
Summary of previous reports of coexisting Fabry disease and IgA nephropathy and their clinical characteristics.

References	Year	No.	Country	Sex	Age	Proteinuria	Hematuria	ERT	Trans	Other therapy
Yang et al ^[3]	2017	6	China	M4/F2	30.5	Y (M4, F2)	Y (M1, F0)	–	–	ACEI/ARB
Jun ^[4]	2016	3	China	M2/F1	20/30/28	Y (M, M, –)	Y (M, M, F)	–	–	–
Kim et al ^[5]	2015	1	China	M1	45	Y	Y	+	–	Prednisolone + eprosartan
Xiejia ^[6]	2015	2	China	M1/F1	38/31	Y (M, F)	Y (–, F)	–	–	–
Caihong ^[7]	2015	1	China	F1	33	Y	N	–	–	–
Yin et al ^[8]	2014	2	China	M2	54/33	Y (M, M)	Y (M, –)	–	–	Valsartan (M, M)
Maixnerova et al ^[9]	2013	2	Czech	M1/F1	26/30	Y (M, F)	Y (M, F)	+	+	Hemodialyse + corticosteroid (M)
Chao et al ^[11]	2012	1	China	M1	49	Y	–	+	–	–
Kakita et al ^[2]	2010	1	Japan	F1	50	Y	Y	+	–	Enalapril
Shimohata et al ^[10]	2009	1	Japan	M1	22	Y	N	+	–	Dipyridamole
Whybra et al ^[12]	2006	2	German	F2	16/1	Y (F, F)	Y (F, F)	+	–	(F, F)
Pisani et al ^[13]	2005	1	Italian	F1	52	Y	Y	+	–	–
Kawamura et al ^[14]	1997	1	Japan	M1	28	Y	Y	–	–	Prednisolone + cyclophosphamide
Yoshida et al ^[15]	1994	1	Japan	F1	32	Y	Y	–	–	–

ACE=angiotensin converting enzyme, ARB=angiotensin receptor blocker, ERT=enzyme replacement therapy, F=female, M=male, N=no, Y=yes.

Alport syndrome results from the mutation of the $\alpha 3$, $\alpha 4$, or $\alpha 5$ chain of type IV collagen fiber, and presents as proteinuria, anterior conization of lens and hearing impairment. Clinically, patients with Alport syndrome may have anterior conization of lens and hearing impairment, which are not observed in those with FD. Our patient did not have hematuria, vision or hearing impairment, and staining for type IV collagen fiber was intact, unlike in those with Alport syndrome. From the pathological perspective, characteristic microscopic findings of FD, such as podocyte enlargement with small and uniform vacuolization resulting from glycosphingolipid accumulation, were not seen in our patient, and interstitial foamy cell infiltrations tend to be a specific pathology of Alport syndrome. These foamy cells derive from either interstitial macrophages engulfing sphingolipid or heavily vacuolized tubular epithelia infiltrations. Electron microscopy plays an important role in the differential diagnosis of FD, and massive sphingolipid accumulation in podocytes was found in this patient, supporting our diagnosis.

In conclusion, FD coexisting with IgAN is rare and may have non-specific clinical presentations. Negative family history is noted among 5% of the involved patients. The diagnosis of these patients relies on examination of renal biopsy specimens, using light microscopy, immunofluorescence, and electron microscopy, and genetic diagnosis is needed for confirmation. More mechanistic studies are needed to determine the presence or absence of a shared pathophysiology between FD and IgAN.

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