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Case Report

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Fabry Disease Presenting as End-Stage Kidney Disease

Madeleine V. Pahl[a] Jean Hou[b]

[a]Division of Nephrology and Hypertension, University of California Irvine, Orange, CA, USA; [b]Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Keywords
Fabry disease · Proteinuria · End-stage kidney disease · Chronic kidney disease · Rare disease

Abstract
Background: Fabry disease (FD) is an X-linked disorder due to a pathogenic variant of the *GLA* gene that codes for the alpha-galactosidase enzyme. The reduced or absent activity of the enzyme results in lysosomal accumulation of globotriosylceramide and its derivative, globotriaosylsphingosine, in a variety of cells, leading to a variety of complications including cardiac, renal, and cerebrovascular disorders. Early diagnosis is critically important for the selection of therapeutic treatments, which are essential for improving outcomes. Here we present a case of FD diagnosed at the time of end-stage kidney disease presentation. ***Summary:*** A 40-year-old man with a history of seizures presented with increased serum creatinine, nephrotic rage proteinuria, and new-onset hypertension. A renal biopsy revealed numerous, whorled, and lamellated cytoplasmic inclusions in podocytes, glomerular peritubular capillary endothelial cells, mesangial cells, arterial myocytes, and interstitial macrophages. Ultrastructural analysis confirmed the presence of glycosphingolipid inclusions and enlarged lysosomes packed with multi-lamellated structures ("zebra" bodies). The findings were suggestive of a lysosomal storage disorder, and testing for alpha-galactosidase A levels revealed near-absent enzyme activity, confirming the diagnosis of advanced FD. ***Key Messages:*** The diagnosis of FD can be challenging as the manifestations of the disease are nonspecific, and patients can present early with classical symptoms or late with non-classical patterns of involvement. We will discuss strategies to identify the disorder early by reviewing the classical and non-classical presentations and further outline currently available and potential future treatment options.

Case Presentation

A 40–45 year-old man was hospitalized because of a creatinine (Cr) of 11.1 mg/dL and new-onset hypertension noted during a primary care evaluation. Several years prior, his Cr was known to be 1.2 mg/dL, and several months before the recent evaluation, he had noted several mildly elevated blood pressures (BPs) of 140s/90s mm Hg. The patient denied any symptoms of headache, chest pain, shortness of breath, edema, nausea, vomiting, reduced appetite, or any previous history of kidney disease. He had used naproxen sodium 220 mg rarely as needed for occasional headaches. He had a past medical history of a seizure disorder and was maintained on lamotrigine 150 mg twice daily. His seizure disorder was currently well controlled, and during evaluation of that problem, he was noted to have nonspecific white matter changes on brain MRI imaging. The rest of his review of symptoms was negative. He denied extremity pain or any gastrointestinal complaints. His family history was positive for hypertension and type 2 diabetes mellitus, but he had no renal disease or other medical problems. His physical exam was normal except for a BP of 163/107 mm Hg and the presence of multiple small, dark red lesions in

karger@karger.com
www.karger.com/gdz

Correspondence to:
Madeleine V. Pahl, mpahl@uci.edu

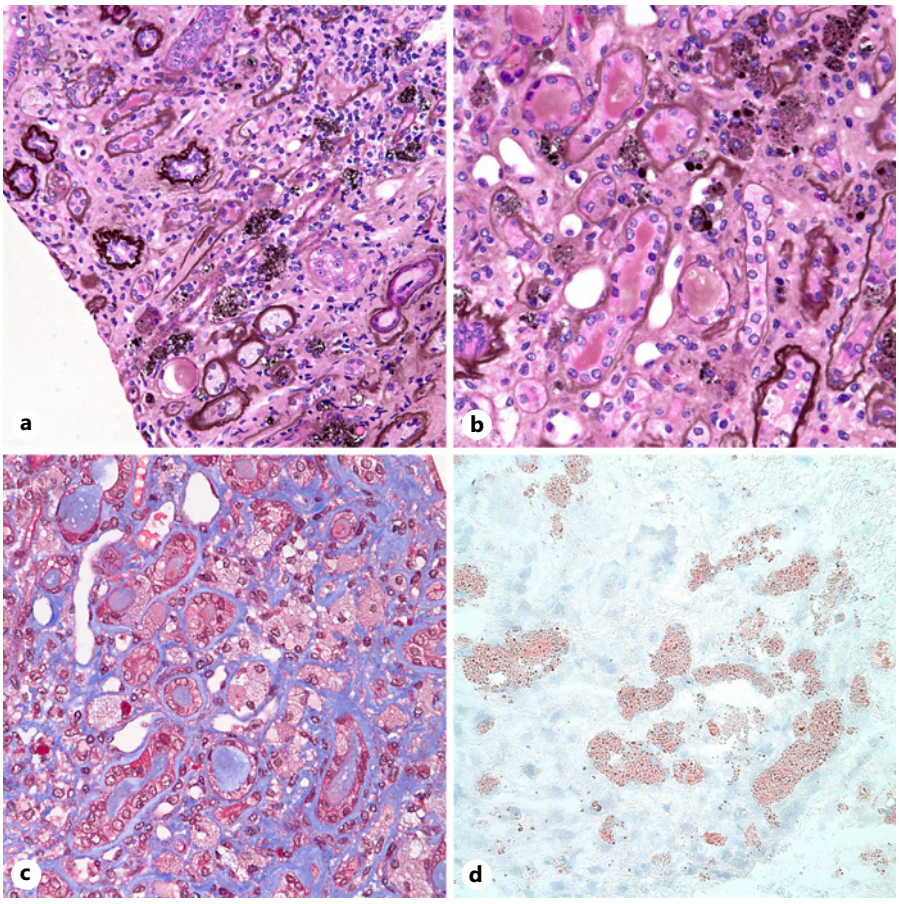

Fig. 1. Light microscopic findings. The tissue submitted for light microscopy consisted of superficial medulla without glomeruli. On closer examination, Jones methenamine silver stain revealed the presence of rounded silver-positive inclusions within the cytoplasm of peritubular capillary endothelial cells, tubular epithelial cells, and likely interstitial macrophages (**a**, **b**; magnification ×200 and ×400, respectively). Masson's trichrome stain revealed the presence of cytoplasmic vacuoles in a similar distribution as the silver-positive inclusions (**c**; magnification ×400). An oil red O stain (for lipid), performed on the frozen tissue, showed positivity within likely peritubular capillary and tubular epithelial cells (**d**; magnification ×400).

the lower abdomen and extremities. Initial laboratory data revealed a serum Cr of 11.1 mg/dL, glucose of 72 mg/dL, albumin of 3.9 g/dL, a urine analysis with 1+ blood, 2+ protein, and a urine protein/Cr ratio of 4.9 g/g. Serologic evaluation was non-diagnostic, and a renal ultrasound revealed normal-sized kidneys with thin echogenic cortices and multiple simple cysts. To determine the cause and extent of his kidney disease, he underwent a renal biopsy.

Pathology Presentation

The specimen for conventional light microscopy consisted of scant fragments of severely scarred cortex which contained a single globally sclerotic glomerulus; no preserved glomeruli were present for evaluation. Jones methenamine silver stain revealed numerous silver-positive cytoplasmic inclusions in tubular epithelial cells, interstitial macrophages, and few peritubular capillary endothelial cells (shown in Fig. 1a, b). Trichrome stain revealed prominent cytoplasmic vacuolization in the same distribution as the silver-positive inclusions (shown in Fig. 1c). There was near-total tubular atrophy and interstitial fibrosis in the very scant cortex sampled, and one artery displayed moderate intimal fibrosis. While the severe parenchymal scarring and moderate arteriosclerosis could account for the elevated serum Cr, there was insufficient material to determine a morphologic cause for the nephrotic-range proteinuria. The possibility of unsampled secondary focal segmental glomerulosclerosis was a consideration, but no definitive diagnosis could be rendered.

The tissue submitted for immunofluorescence microscopy contained seven globally sclerotic glomeruli; no preserved glomeruli were available for evaluation. As such, the possibility of immune complex or complement-mediated glomerular diseases such as membranous nephropathy could not be excluded at this point, and electron microscopy was pending to evaluate for the presence of glomerular deposits (if any) or ultrastructural abnormalities that might account for the nephrotic range proteinuria. Given the extensive cytoplasmic vacuolization noted by light microscopy, a special stain for lipid was performed with oil red O and revealed positive staining within the epithelial cell vacuoles, consistent with

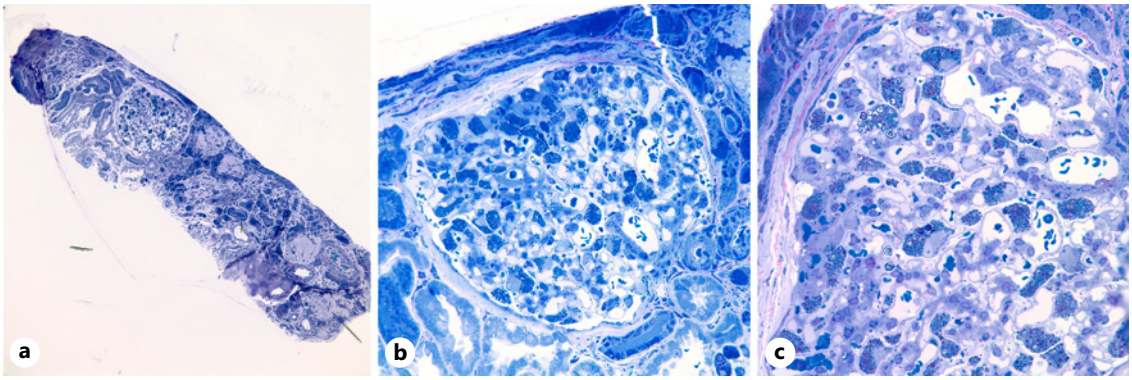

Fig. 2. The specimen for electron microscopy, stained with methylene blue, revealed a small portion of cortex with severe parenchymal scarring and globally sclerotic glomeruli (**a**; magnification ×40). The only preserved glomerulus in the entire biopsy was identified in this tissue and contained numerous, rounded methylene blue-positive inclusions within the cytoplasm of podocytes (**b**; magnification ×400). Few of the podocyte inclusions appeared to be whorled and lamellated (**c**; magnification ×600).

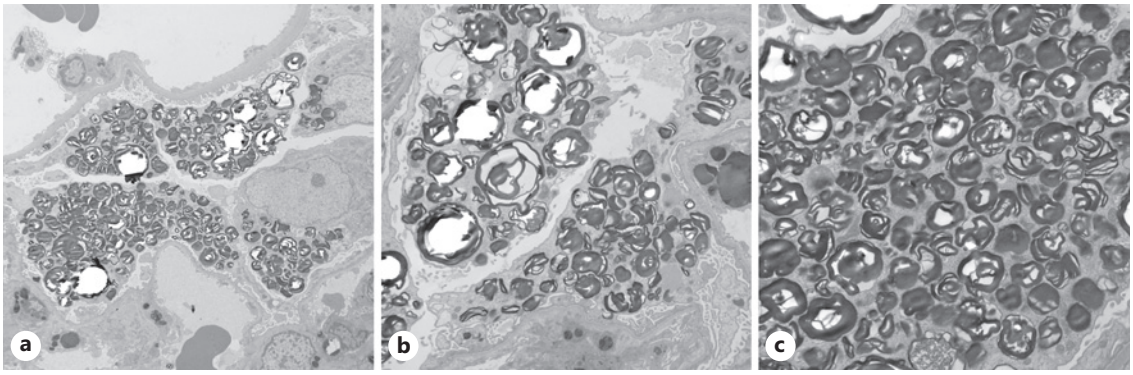

Fig. 3. Ultrastructural evaluation of the single glomerulus confirmed the presence of numerous atypical lipid inclusions within the podocyte cytoplasm. The electron-dense inclusions were rounded and whorled, sometimes with a characteristic lamellated appearance known as "myelin bodies" (**a**, **c**; magnification ×4,000 and ×12,000, respectively). The inclusions displayed variability in size, ranging from small to quite large (**b**; magnification ×4,000).

lipid accumulation (shown in Fig. 1d). Oil red O is a nonspecific stain for lipid and positive staining is not diagnostic for any particular lipid or lysosomal storage disease. However, accumulation in an abnormal distribution (in podocytes or peritubular capillaries, for example) may indicate abnormal lipid metabolism.

The specimen for electron microscopy consisted of a scant fragment of renal cortex containing six glomeruli, five of which were globally sclerotic. The only preserved glomerulus in the entire biopsy was identified, which was considerably enlarged but with an otherwise unremarkable glomerular tuft (shown in Fig. 2a). Glomerulomegaly, as a sequela of hyperfiltration, is a risk factor for secondary focal segmental glomerulosclerosis, although the degree of proteinuria in this patient would be somewhat atypical for a secondary lesion. Notably, the podocytes in this intact glomerulus as well as the globally sclerotic glomeruli contained numerous, prominent, rounded, whorled, and lamellated methylene blue-positive cytoplasmic inclusions (shown in Fig. 2b, c). Similar inclusions were also noted within glomerular peritubular capillary endothelial and mesangial cells, arterial myocytes as well as numerous interstitial macrophages. Ultrastructural analysis confirmed the presence of prominent osmiophilic, concentrically lamellated, whorled inclusions ("myelin" bodies) consistent with

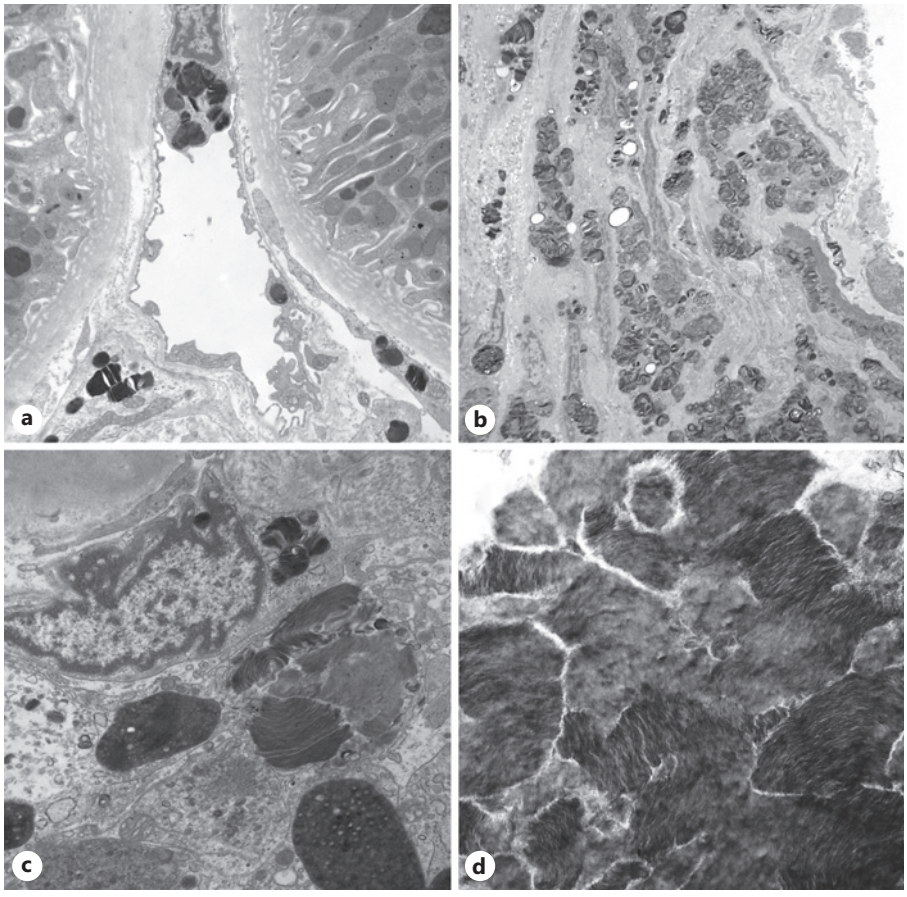

Fig. 4. Ultrastructural evaluation revealed the presence of the atypical lipid inclusions also within the cytoplasm of peritubular capillary endothelial cells (**a**; magnification ×12,000) and arterial myocytes (**b**; magnification ×5,000). Unlike the whorled myelin bodies observed most frequently in the podocytes, these lipid inclusions displayed distinctive layering and lamellations with a stacked configuration at varying angles, known as "zebra bodies" (**d**; magnification ×50,000). The zebra bodies were most frequently observed within larger membrane-bound structures morphologically consistent with lysosomes (**c**; magnification ×20,000).

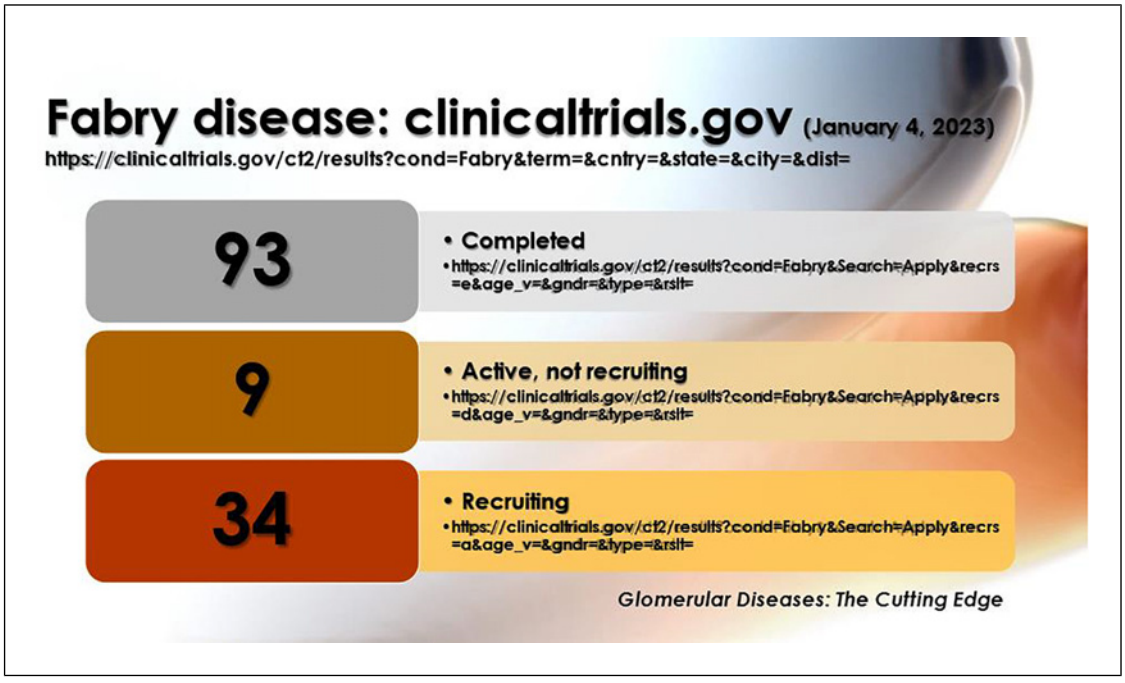

Fig. 5. Links to available clinical trials of FD on clinicaltrials.gov.

glycosphingolipid inclusions in the cytoplasm of podocytes (shown in Fig. 3a–c). These ultrastructural inclusions were also present in the cytoplasm of peritubular capillary endothelial cells (shown in Fig. 4a) and vascular smooth muscle cells (shown in Fig. 4b). The cytoplasm of proximal and distal tubular epithelial cells, mesangial cells, and glomerular capillary and peritubular endothelial cells also contained numerous enlarged secondary lysosomes packed with multi-lamellated structures ("zebra" bodies) (shown in Fig. 4c, d), some of which were admixed with vesicular structures with a heterogeneous appearance. Similar cytoplasmic inclusions were also noted in vascular myocytes. Unfortunately, there were no preserved glomeruli present in this biopsy; however, if present, one expect to find finely vacuolated/foamy cytoplasm in the podocytes typical of Fabry disease (FD) renal involvement. The findings in this patient's biopsy were highly suggestive of a lysosomal storage disorder, and testing for alpha-galactosidase A levels was performed. The test revealed near-absent enzyme activity, confirming the diagnosis of advanced FD and establishing a cause for the patient's chronic kidney disease (CKD) and nephrotic-range proteinuria.

Treatment and Follow-Up

After the report of the renal biopsy was received, our patient had leukocyte α-GAL activity measurement which showed <1% enzyme activity. He was referred to the genetics team for consultation and genetic analysis for himself and his family. Genetic testing revealed a mutation consistent with FD, and he was started on agalsidase-beta. He was prepared for hemodialysis and was referred for kidney transplant. The patient is now on post-living related renal transplant status with a stable clinical course.

Conclusion

FD, also known as Fabry-Anderson disease, is the most prevalent of the lysosomal storage diseases. It is an inborn error of glycosphingolipid metabolism due to a pathogenic variant in the GLA gene, located in the *X* chromosome, that codes for alpha-galactosidase enzyme (α-GAL). The markedly reduced or absent activity of the enzyme results in lysosomal accumulation of globotriosylceramide (Gb3) and its derivative, globotriaosylsphingosine (lyso-Gb3), in a variety of cells, leading to the many manifestations of the disorder, including cardiac, renal, and cerebrovascular effects [1]. The prevalence of the disorder is estimated to range from 1:8,454 to 1:117,000 in males [2], and although rare, it can result in progressive CKD and end-stage kidney disease (ESKD). Early diagnosis and comprehensive evaluation of affected individuals are critically important for the selection of current and evolving therapeutic treatments, which are essential for improving outcomes [3, 4]. The diagnosis of FD can be challenging as the manifestations of the disease are nonspecific, and patients can present early with classical symptoms or late with non-classical patterns of involvement. An incorrect diagnosis is often made initially, and the delay to the correct diagnosis after symptom onset has been estimated to be 13.7 years in men and 16.3 years in women [5]. The diagnosis of FD can be made when very low α-GAL enzyme activity is noted in men and confirmed in both men and women with appropriate genetic testing.

The variety in the disease presentation is mostly due to the type of mutation in the GLA gene and sex of the patient. Given X-linked inheritance, men are generally more severely affected than women. Classical forms of the disease are typically found in men with less than 1% α-GAL enzyme activity, caused by different types of genetic rearrangements, splicing defects, and missense or nonsense variants. Men with more than 1% enzyme activity may have missense or splicing variants and have a late presentation. In women, the enzyme activity may be within the normal range, and the classification of the presentation is likely related to the type of mutation, random X-chromosome inactivation with some cells having the defective gene activated while others have the functioning gene, family history, and other biochemical characteristics [6, 7].

Patients can present with a spectrum of clinical manifestations at different ages. Approximately 80% of men have neurologic involvement by their 20s, and kidney and cardiac involvement by their 50s [5]. However, some with atypical variants may present later in life.

Classic FD, the most severe phenotype, can present with neuropathic limb pain in children. If the diagnosis is not known to other family members, the cause is often unrecognized, and the child is thought to have psychosomatic events. Angiokeratomas and telangiectasias are frequently seen, typically in the groin, hip, and periumbilical areas, and can provide important physical examination clues that can lead to the correct diagnosis. Heat and cold intolerance and hypohydrosis occur early and tend to worsen in early adulthood. Gastrointestinal symptoms are also frequently seen and often consist of abdominal pain, nausea, vomiting, diarrhea, or

constipation. Patients are frequently diagnosed as having irritable bowel syndrome. Corneal opacities, corneal verticillate can be seen relatively early, and while they are not associated with visual impairment, they can provide a clue to the diagnosis. Patients can also manifest pulmonary involvement with asthma or chronic bronchitis. Osteopenia and osteoporosis have also been reported. Hearing loss is also not uncommon, and a variety of psychological manifestations such as anxiety, depression, and chronic fatigue are also frequently seen [8]. Cerebrovascular manifestations include transient ischemic attacks and ischemic strokes and can be seen in about 25% of patients in their 40s [9]. Progressive cardiac involvement is seen in adults and can present as concentric left ventricular hypertrophy, myocardial fibrosis, heart failure, coronary artery disease, aortic and mitral valve abnormalities, aortic root dilatation, conduction abnormalities, and arrythmias. Interestingly, hypertension can be a late presentation, is seen in about 30% of cases, and appears to present after the development of CKD [10].

Renal involvement is common and occurs in 50% of men with classic disease by their mid-30s and in 20% of women by the sixth decade. It typically consists of kidney function impairment and proteinuria. It can less commonly present with isosthenuria, polydipsia, and polyuria. On imaging, renal sinus cysts can be seen. The proteinuria initially is >200 mg/day and increases with progression of CKD. However, nephrotic-range proteinuria is infrequently seen. In untreated patients with proteinuria, CKD progresses to ESKD over an average of 4 years [10].

Attention to medications that can exacerbate renal dysfunction in this group of patients is an important part of management. Episodes of neuropathic pain are often self-treated with non-steroidal anti-inflammatory agents [11] and thus the role of these agents in the progression of CKD should be carefully addressed. Medications shown to be effective in management of neuropathic pain, such as gabapentin, are recommended as first-line treatment and are the preferred modalities for pain crisis management [12].

FD should be suspected, and genetic testing should be provided to those with CKD, particularly men with a family history of disease, with no definitive diagnosis and when no renal biopsy has been performed. The difficulty in recognizing this condition and the identification late in its presentation can only be reversed by the introduction of widespread screening of at-risk patients.

Treatment of FD was revolutionized with the introduction of enzyme replacement therapy (ERT) more than 15 years ago, and currently, there are several new treatment developments undergoing clinical trials. The goals of therapy are to slow or prevent the progression of the disease that results in irreversible tissue damage and consists of Fabry-specific therapy with the addition of adjunctive therapies for the neurologic, cardiac, or kidney complications. Currently available FD-specific treatment options include 2 forms of ERT, agalsidase-alpha and agalsidase-beta. Only the beta formulation is approved in the USA. For males with classic FD, expert opinion suggests early initiation with ERT or chaperone therapy where indicated. ERT has been shown to reduce Gb3 levels in renal endothelial cells, tubular and mesangial cells, and podocytes [13]. Long-term studies have shown small but significant beneficial effects of ERT on cardiovascular and renal complications, with some superiority of the higher dosed beta preparation [14].

Migalastat is another Fabry-specific therapeutic option. It is an oral agent that acts as a chaperone by binding and stabilizing specific mutant forms of α-GAL which then allows its movement into lysosomes and results in increased enzyme activity. It can be used as first-line therapy in those with amenable GLA mutations and an estimated glomerular filtration rate >30 mL/min/1.73 m^2 [15].

Renal supportive care for patients with FD is similar to that provided to those with CKD from other causes. Hypertensive patients with proteinuria (>500 mg/day) should be treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker [16]. Whether renin-current Kidney Disease: Improving Global Outcomes (KDIGO) treatment recommendations for the disease entity angiotensin system blockade are beneficial in those with normal BP or proteinuria <500 mg a day is not known and treatment should be individually assessed. Patients who develop ESKD can be managed with hemo- or peritoneal dialysis. ERT is typically continued; however, it is unclear if survival is improved. FD patients are potential candidates for kidney transplantation, and allograft and patient outcomes appear comparable to those with other ESKD causes [17]. While there are no current KDIGO treatment recommendations for FD, the evaluation and management of adult and pediatric patients have recently been reviewed, discussed, and published by expert panels from KDIGO groups [18] and a European panel of experts [19]. Additionally, physicians should be aware of several associations and online sources available to their Fabry patients, such as the Fabry Support and Information Group (FSIG; https://fabry.org) and the National Fabry Disease Foundation (NFDF; https://www.fabrydisease.org).

There are several new developments for the treatment of FD that are currently being actively explored (shown in Fig. 5). Second-generation enzyme replacement therapies have been developed and are undergoing human clinical trials. Pegunigalsidase-alfa is produced in plant cells (tobacco) and has been modified with polyethylene glycol to reduce clearance and stabilize the enzyme. Phase I/II clinical trials demonstrated a mean half-life of 80 h, much longer than the <1 h half-life of agalsidase-beta. Phase III clinical trials [20] have recently been completed, and the drug has just received US FDA approval this May of 2023. Moss-aGal is another plant-based recombinant α-GAL that may result in higher renal tissue enzyme activity. A phase I trial has been completed with good safety results, and preparations are being made for phase II/III trials [21]. Substrate reduction therapy, a way to reduce the availability of the compound that cannot be degraded due to the enzymatic defect, is another treatment approach that is being explored. In those with residual enzyme activity, these oral agents may be adequate to reduce the production of the substrate to levels that can be managed by the existing enzyme activity. Additionally, these small molecules do not induce anti-drug antibodies like ERT products and may cross the blood-brain barrier. Currently, two such agents are undergoing clinical trials: Venglustat (Sanofi Genzyme) and Lucerastat (Idorsia Pharmaceuticals). Both inhibit glucosylseramide synthase and reduce Gb3 and lyso-Gb3 levels [4].

Gene therapy, accomplished by delivering viral vectors containing an inserted copy of the human GLA gene, transduces the recipient's cells to express a corrective copy of α-Gal. Currently, methodologies using lentiviral and adeno-associated viral vectors are undergoing clinical trials. Freeline Therapeutics and Sangamo Therapeutics have initiated phase I/II clinical trials studying the effect of adeno-associated viral-mediated gene therapy on hepatic production and secretion of α-GAL using liver-specific promoters. These treatments have already been shown to result in over-expression of plasma α-GAL and have been well tolerated. The challenge will be to see if these enzyme levels are adequate to target all affected cells and tissues, be long standing, and not be associated with significant antibody production [4].

Statement of Ethics

This case presentation that does not include any patient identifiers is being provided for educational purposes only. Ethical committee approval is not required in accordance with local and national guidelines. The authors do not have the patient consent to publish the case and this requirement was waived by their Local IRB/Ethical Committee.

Conflict of Interest Statement

Madeleine V. Pahl is funded by Sangamo Therapeutics, Inc. Jean Hou has no conflicts of interest to declare.

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Author Contributions

Madeleine Pahl and Jean Hou both contributed equally to the preparation of the case presentations and treatment follow-up sections. Jean Hou prepared the pathology section, and Madeleine Pahl prepared the discussion.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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