CASE REPORT

Anderson-Fabry disease: diagnostic problems from gastrointestinal manifestations to the diagnosis of kidney disease

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KEY WORDS

Anderson-Fabry disease, chronic diarrhea, chronic kidney disease, hypertrophic cardiomyopathy, proteinuria

ABSTRACT

We report a case of a 52-year-old male who has been diagnosed for many years because of chronic diarrhea and proteinuria with concomitant gradually progressing chronic kidney disease. Diagnostic problems associated with the initial diagnosis of amyloidosis as a primary cause of the patient's complaints have been described. Anderson-Fabry disease (AFD) was suspected following comprehensive evaluation that resulted eventually in the exclusion of amyloidosis and the echocardiographic examination showing hypertrophic cardiomyopathy in the patient with no history of hypertension and aortic valve defects. The diagnosis of AFD was confirmed by results of enzymatic tests.

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INTRODUCTION Anderson-Fabry disease (AFD) remains the second most common congenital storage disease, characterized by deficiency of a lysosomal enzyme, α-galactosidase A. This defect results in progressive intracellular accumulation of glycosphingolipids, mainly globotriaosylceramide. Because the defective DNA fragment coding for α-galactosidase is located on the X chromosome (q22.11), AFD predominantly affects males, although it is thought that even 30% of heterozygotic females with the mutation of this gene may demonstrate clinical manifestations of this disease during their lifetime.[1]

When AFD remains undiagnosed and a causal treatment not initiated, the disease is progressive, leading, among others, to heart, kidney and nervous system damage.[2,3]

The disease was for the first time described in patients with characteristic skin lesions, i.e. angiokeratoma and proteinuria, already in 1898 by Johannes Fabry and William Anderson. It is now estimated that the disease manifestations occur in 1 for 100,000 to 400,000 persons, although due to extremely variable clinical presentation and diverse manifestations from different organs over varying periods of time, the data are probably underestimated.

Natural history of the disease shows typically that the first symptoms, arising already in childhood, are burning paroxysmal hand and foot pains (acroparesthesias) and disorders of sweat secretion leading to impaired thermoregulation. Several years later, typical skin lesions (angiokeratoma) appear mainly on the hips, thighs and crotch, which are accompanied by gastrointestinal symptoms, including abdominal pain, nausea and diarrhea.

AFD is most commonly diagnosed in a patient's thirties and forties, when symptomatic heart failure and arrythmias develop in association with neurological and eye symptoms. Moreover, kidneys become affected and glomerular filtration is progressively decreased.[4]

The current paper discribes a case of a 52-year-old male who was referred to the Nephrology University Clinic to establish a diagnosis of proteinuria and stage 3 chronic kidney disease.

CASE REPORT In June 2007, the patient was admitted to the Department of Nephrology,

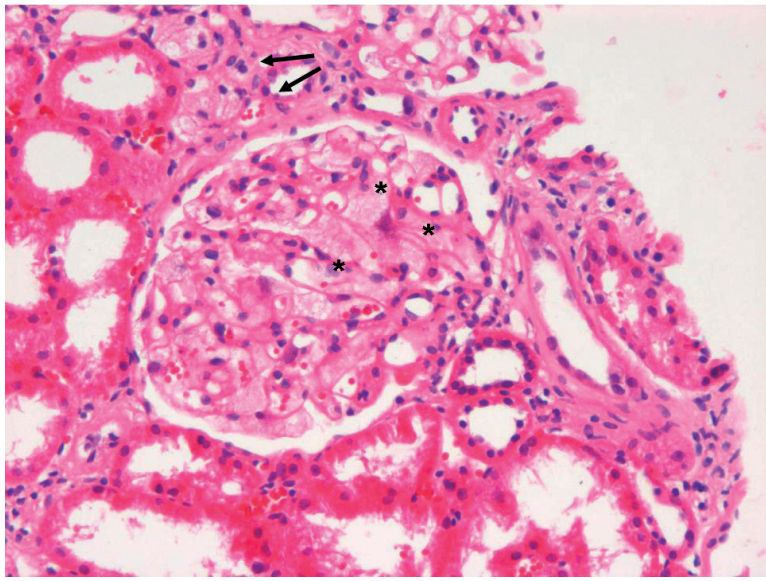

FIGURE 1 Biopsy specimen of the Anderson-Fabry disease patient. Renal glomerulus with enlarged tubular cells containing numerous small cytoplasmic vacuoles. Lesions involving mainly podocytes (marked with asterisks) and single tubules (marked with arrows). Hematoxylin and eosin staining, 20×

FIGURE 2 Enlarged cells (marked with asterisks) of tubular epithelium and small vacuoles in the cytoplasm. Hematoxylin and eosin staining, 40×

Hypertension and Internal Diseases at the University Hospital in Bydgoszcz to diagnose proteinuria (daily protein loss [DPL] 2–7 g/24 h) with concomitant mild hypoalbuminemia (serum albumin 3.22 g/dL) and impaired glomerular filtration (glomerular filtration rate [GFR] according to Modification of Diet in Renal Disease [MDRD] 42 ml/min/1.73m^2, i.e. stage 3 chronic kidney disease).

The main complaint of the patient, apart from periodic lower extremity edema, was chronic diarrhea occurring since childhood (several loose, watery stools per day, without blood and mucus) and a progressively impaired exercise capacity.

Diarrhea that worsened frequently have been the cause of multiple hospitalizations at internal medicine wards for approximately 20 years. The patient self-reported that as early as during his first stay in hospital in 1985 proteinuria was diagnosed (not documented in medical records).

Over the next years, several upper endoscopic examinations showed chronic gastritis and hiatal hernia. Colonoscopy was normal. In 2000, histopathologic examination of gingival biopsy specimens demonstrated amyloid deposits, although the biopsy of the colon mucosa taken in 2001 did not confirm these findings. At the same time, in a local clinic, diarrhea treatment and pancreatin therapy were introduced to relieve the complaints, resulting in some improvement.

In April 2004, the patient was referred from a local clinic to the Department of Gastroenterology to establish the diagnosis with assistence of specialists. Amyloidosis, microscopic polyangitis and celiac disease were considered in differential diagnosis.

Gastroscopy and colonoscopy performed again at that time and analysis of numerous specimens showed only characteristics of chronic inflammation of the stomach mucosa. Because of pain in metacarpophalangeal joints, a radiograph was performed and demonstrated degenerative lesions.

Proteinuria (DPL 2.0 g/24 h), normal results of endoscopic tests and lack of other indicators of malnutrition syndrome resulted in the the exclusion of exudative enteropathy. The working hypothesis of amyloidosis was not eventually confirmed. However, higher creatinine levels (118.4 μmol/l, GFR according to MDRD 59 ml/min/1.73 m^2) were noted and the patient was referred for further nephrological evaluation.

In January 2005, the patient was hospitalized for the first time at the nephrological ward to diagnose proteinuria (DPL 2.5 g/24 h, no active urinary sediment, serum albumin 3.46 mg/dl). Laboratory tests did not show monoclonal protein in serum or in urine. The gingival mucosa specimen was taken again to confirm or rule out the presence of amyloid. Since amyloid deposits were detected in the specimen and poorly differentiated renal cortex and medulla on ultrasonography (with normal size of the kidneys, i.e. left kidney 117 × 48 mm, right kidney 121 × 62 mm), the diagnosis of amyloidosis was reestablished as a probable cause of proteinuria and diarrhea. Furthermore, immunological tests were performed (anti-nuclear antibodies, perinuclear-staining anti-neutrophil cytoplasmic antibodies, cytoplasmic-staining anti-neutrophil cytoplasmic antibodies, anti-gliadin IgA and IgG antibodies, anti-endomysium IgA antibodies [EmA], all results were negative) and excluded other causes of proteinuria and chronic diarrhea.

In 2007, proteinuria increased to 7.1 g/24 h with concomitant progression of chronic kidney disease. In 1985, laboratory tests showed serum creatinine 79.5 μmol/l, whereas in 2007 it was 159 μmol/l (GFR according to MDRD was 100 and 42 ml/min/1.73 m^2, respectively). During the stay in the center, proteinuria was regularly measured. On admission physical examination, there were mild lower extremity edema, blood pressure was 115/70 mmHg (the patient

was taking losartan 1 × 25 mg/24 h), heart rate was 60/min, interrupted by single extrasystolic beats (ECG – sinus rhythm interrupted by single supraventricular extrasystoles, left ventricular hypertrophy and overload, the Sokolov-Lyon index was 63 mm; in the available medical records at discharge from hospital the characteristics of myocardial hypertrophy have already been reported since 1997).

Repeated histopathology of gingival and rectal specimens excluded amyloidosis. Previous diagnostic evaluation was expanded by bone marrow examination, which yielded normal results. Echocardiography showed left ventricular hypertrophy (left ventricle diameter was 4.7 cm, posterior wall thickness 1.9 cm and ventricular septum 2.4 cm), suggesting non obstructive hypertrophic cardiomyopathy. Due to increasing proteinuria and progression of chronic kidney disease, the kidney biopsy was performed, however, a lack of glomeruli in the specimen made it impossible to interpret the result. On the basis of the whole clinical presentation (hypertrophic cardiomyopathy, chronic kidney disease, chronic diarrhea) a suspicion of AFD was for the first time made. Ophthalmological examination showed features of incipient cataract without typical corneal lesions. Enzyme activity measured in the Institute of Psychiatry and Neurology in Warsaw confirmed the diagnosis because α-galactosidase in leukocytes was 0.16 nmol/mg protein/h (normal value: 9.0 ±2.4), in serum – 0.15 nmol/ml/h (normal value: 8.6 ±1.5), while β-galactosidase as a control enzyme was 174 nmol/mg protein/h; (normal value: 163 ±99). The patient with his daughter and three sisters were referred for molecular testing that demonstrated that all females were carriers of the defective gene.

In February 2008, the patient was hospitalized in the Institute of Cardiology in Warsaw. Because of atrial fibrillation with rapid ventricular rate and simultaneously pauses up to 2.6 s upon administration of a small dose of β-blocker, after electrical cardioversion the patient had a dual chamber pacemaker implanted, which made it possible to add β-blocker to prior therapy.

In March 2008, the renal biopsy was performed again. Histopathology of a kidney biopsy specimen showed highly advanced lesions within renal glomeruli in the form of numerous big cells with large empty vacuoles (pathognomic characteristics of AFP). The lesions involved nearly all glomerular cells, including, first of all, podocytes (FIGURE 1). Moreover, lesions similar to those in glomeruli were found in the renal tubular epithelial cells. They were considerably expanded cells containing numerous vacuoles (FIGURE 2). The lesions were most distinct in the lower section of Henle's loop. Endothelium with vacuoles was found in blood vessels in the renal stroma.

DISCUSSION The case of AFD presented here, although matching the characteristic manifestation of this nosological entity, arose considerable diagnostic concerns. Diarrhea occurring since childhood initially directed the diagnosis only towards gastroenterological diseases and proteinuria (150 mg/dl in a single urine sample) in the first years of the disease, misjudged as low-degree, was ignored. In the patient's history there was no data on skin lesions and paroxysmal acroneuropathy manifesting as hand and foot pains, which in a natural history of the disease appear in the first place. Chronic diarrhea reported by the patient could be one of manifestations of damage to the autonomous and endocrine systems.[5,6] Gastrointestinal symptoms usually occur in 50–90% of cases in young adults and become more pronounced with age. Apart from diarrhea, patients commonly report nausea, vomiting, and additional examinations could show features of esophageal achalasia or confirm diverticulosis, being sometimes a cause of perforation.[7]

In the case described in the paper, the hypothesis that amyloidosis underlies the patient's signs and symptoms has hindered establishing the final diagnosis for several years. On one hand, such a diagnosis might have been supported by chronic diarrhea, which could be associated with amyloid deposition in the extracellular space, leading to the impairment of vegetative or pancreatic exocrine function. On the other hand, myocardial involvement, so characteristic of amyloidosis, manifests itself as restrictive cardiomyopathy, and not hypertrophic cardiomyopathy observed in the patient (and typical of AFD). Moreover, a delay in establishing the diagnosis of AFD was the consequence of lack of a critical approach towards the positive result of the gingival specimen evaluation for the presence of amyloid, with no features of amyloidosis in the samples of the gastrointestinal tract, which remains the only reference location apart from the subcutaneous tissue of the abdomen. Although proteinuria in the course of amyloidosis may be of various degree, the most characteristic remains nephrotic proteinuria with concomitant severe hypoalbuminemia.[8]

It should be emphasized that the final exclusion of amyloidosis made in the Department by additional tests for monoclonal gammapathies as causes of immunoglobulin light chain-derived amyloidosis, was essential before the decision on the kidney biopsy has been made. This procedure confers a high risk of life-threatening bleeding because of potential amyloid infiltration of the blood vessels and decreased factor X activity.

Results of echocardiographic examination confirming hypertrophic cardiomyopathy, especially in a patient without a history of hypertension (recommendation to take losartan for nephroprotection) and an aortic valve defect, and with concomitant chronic kidney disease and diarrhea, substantiated the suspicion of AFD, which was finally confirmed by measurement of α-galactosidase activity. The kidney biopsy showed not only lesions characteristic of AFD, but also assessed significant local progression of the disease, which

should have additionally argue for the decision on an urgent initiation of substitution treatment with β-agalsidase, which should be imitated shortly. Despite poor prognosis in AFD that therapy could improve the patient's quality of life and slow down progression of chronic kidney disease leading to renal replacement therapy.[9-11] Treatment with losartan (1 × 25 mg/24 h), release-controlled metoprolol (1 × 75 mg/24 h) and anticoagulant treatment with acenocoumarol (with international normalized ratio control) are continued.

The diagnosis of AFD involved molecular tests of the patient's family. The disease is X-linked recessively inherited, thus the affected father passed the gene to his daughter, who became a carrier, as confirmed by genetic analysis. Unfortunately, all three sisters of the patient also inherited the defective gene from their mother, although there is probability that only half of female offsprings should be carriers.

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