Case Report

Fabry’s disease presenting with oligoanuric end-stage renal failure

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Introduction

Fabry’s disease is an X-linked recessive disorder, caused by the deficiency of the lysosomal enzyme alpha-galactosidase A, leading to systemic deposits of glycosphingolipids such as ceramide-trihexoside [1,2]. Symptoms vary and can be neurological (paresthesias, episodes of severe pain, stroke), cardiovascular (isch-aemic heart disease, dysrhythmias), ocular (corneal dystrophy), cutaneous (angiokeratomas) and renal. Renal involvement is a major manifestation and is characterized by progressive renal failure, which reaches the terminal stage around the fourth decade [3,4].

In this paper we describe a patient presenting with oligoanuric end-stage renal failure whose investigation led to the diagnosis of Fabry’s disease.

Case report

A 35-year-old male reported progressive dyspnea, orthopnea and oedema during the previous 2 weeks. There was no exposure to nephrotoxic agents, infection or any other nephro-urological symptoms. Four years previously the patient underwent accessory AV connection ablation because of pre-excitacion syndrome and paroxysmal supraventricular tachycardia (at that time arterial blood pressure was normal and creatinine was 1.2 mg/dl.). The patient’s mother died at the age of 27 due to an unknown kidney disease.

The results of a physical examination were: blood pressure 220/130 mmHg, T°36.7°C, fundus oculi with mild vascular sclerosis, raised purplish lesions on the scrotal and suprapubic regions and both flanks; the other findings were compatible with congestive heart failure.

Relevant laboratory data were: Hb 9 g/dl, Hto 27%, erythrocyte sedimentation rate (ESR) 140; normal leukocytes, platelet counts and coagulation profile; blood group A Rh+; glucose 6.1 mmol/l (110 mg/dl), urea 52.6 mmol/L (316 mg/dl), serum creatinine 1768 mmol/l (20 mg/dl), Na 136 mmol/l, K 5.5 mmol/l, Cl 107 mmol/l, bicarbonate 14 mmol/l, total Ca 1.72 mmol/l (6.9 mg/dl), P 3 mmol/l, 9.3 mg/dl), uric acid 511.5 mmol/l (8.6 mg/dl). Urinalysis: protein ++; urinary sediment: microhaematuria. Radiography: pulmonary oedema.. ECG and transthoracic echocardiography: left ventricular hypertrophy. Abdominal ultrasound disclosed both kidneys as 10 cm, with increased echogenicity and no hydronephrosis.

The patient presented with oligoanuria and needed emergency haemodialysis with good haemodynamic stability.

The following determinations were normal or negative: AST, ALT, GGT, alkaline phosphatase, CK, LDH, bilirubin, serum electrophoresis, immunoglobulins, HBsAg, HBeAc, anti-HCV, C3, C4, ASTO, RF, RCP, ANA, anti-DNA, aCL, anti-GBM and ANCA antibodies. A 24-h urinalysis gave: protein 2.5 g, glucose 2.14 mmol (390 mg), Na 52 mmol, K 13 mmol; the urine culture was negative.

Kidney and skin biopsies were performed. Kidney biopsy showed diffuse vacuolization of glomerular (Fig. 1) and tubular cells (Fig. 2) that stained with oil-red O; sclerosis and glomerular obsolescence with tubular atrophy and interstitial fibrosis were also seen; non-inflammatory fibrinoid changes, intimal hyperplasia and vacuolated cells appeared in the vessels. The immunofluorescence specimen was positive for Ig M and C3 in glomeruli. The ultrastructural study revealed dense cytoplasmic inclusions, sometimes in a laminated arrangement. Dermal histology was angiokeratomas.

Cornea verticillata was noted after a slit-lamp examination. After specific questioning, the patient reported hypohydrosis and recurrent abdominal pain. Alpha-galactosidase activity in leukocytes from peripheral blood was 62.7 nmoles/min per g of protein (control 1125), while the activity of other acid hydrolases (alpha-fucosidase, beta-galactosidase, alpha and beta mannosidase, acetyl alpha and beta glucosaminidase)
systemic deposition of glycolipids. Deposits in the kidneys are most noticeable in the visceral epithelial cells, although, as we see with this patient, they also affect tubules (especially distal ones), vessels and interstitium [3–5]. These deposits give cells a foamy appearance when studied by light microscopy. The ultrastructural study shows electrondense cytoplasmic inclusions, sometimes with lamellated disposition, zebra bodies [1,3].

From a clinical point of view, nephropathy in Fabry’s disease is first characterized by concentration abnormalities and distal tubular acidosis. Isolated abnormalities in proximal function are also seen, although less frequently [4]. Proteinuria, usually not in the nephrotic range, changes in urinary sediment such as microhaematuria, cylindruria and oval-shaped fat bodies along with arterial hypertension, are common [1]. Renal failure is almost certain in male patients suffering from Fabry’s disease with the end-stage occurring around the fourth decade, although this varies somewhat [4,6]. Given the hereditary nature of this disorder, female carriers will either not develop the disease at all, or will have a mild course. However, cases of women with Fabry’s disease and renal failure have been reported, which can be explained by the Lyon theory on the inactivation of the X chromosome [7,8].

Although the existence of urinary abnormalities cannot be discarded, our patient had normal blood pressure and normal creatinine value for 4 years before admission. This evolution period towards terminal renal failure seems short in Fabry’s disease. It has been suggested that Fabry’s disease is more aggressive in patients with blood types B or AB, given the additional accumulation of glycolipids from group B [8]. Nevertheless, this was not the case for our patient. Nor did the renal biopsy show evidence of another type of nephropathy (systemic lupus erythaematosus, acute interstitial nephritis), which would have accelerated the deterioration of renal function, as has been described [3,9]. It is generally accepted that renal failure in Fabry’s disease is caused by the progressive accumulation of glycosphingolipids, but it is possible that the ischaemia due to vascular lesions plays an important role. On the other hand, as far as we know, the appearance in Fabry’s disease of nephropathy as oligoanuric end-stage renal failure, as occurred in this case, has never been reported.

None of the histological findings, including the ultrastructural ones, is pathognomonic of Fabry’s disease, as similar changes can be observed in GM2 gangliosidosis or in relation to chloroquine or silicon [2,7,10]. For this reason, biochemical confirmation of the alpha-galactosidase A deficit, in the peripheral blood leukocytes or in fibroblasts, is needed for the diagnosis of Fabry’s disease, as was shown in the present case [3,8]. Heterozygous females have a wide range of values as regards enzyme activity, and it is recommended that screening is done by slit-lamp examination and by demonstrating an increase of glycolipids in the urine [7].
The presence of angiokeratoma is a key systemic sign in the diagnosis of Fabry’s disease. They appear as dark red verrucous papules, and are typically found on the flanks, in the scrotal and suprapubic areas. They sometimes look similar to vasculitic lesions, at times they do not appear at all, and may be seen in other entities [2,4,7,8].

Apart from the genetic counselling, the treatment is symptomatic. The effects of alpha-galactosidase replacement are temporary and there is the possibility of side-effects. For uraemic patients, dialysis and a kidney transplant offer acceptable life-expectancy and graft recurrence has not shown to lessen survival [3,6].

This case shows the heterogeneity of the clinical presentation of nephropathy in Fabry’s disease. This disease should be systematically included in the differential diagnosis of patients with kidney disease, a family history of nephropathy or systemic symptoms.

References

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