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Nephropathy by Oxalate Deposits: Not Only a Tubular Dysfunction

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Abstract

Background: Hyperoxaluria may be either inherited or acquired. Primary Hyperoxaluria (PH) is a rare autosomal recessive disease characterized by increased endogenous oxalate production and accumulation in renal and extrarenal tissues. The excess oxalate is excreted in the urine and frequently patients with PH present signs or symptoms related to kidney stones and progressive nephrocalcinosis.

Here we present a case of a young man with an unexplained progressive renal failure, without symptoms of nephrolithiasis or nephrocalcinosis. Renal biopsy examination was performed to clarify renal dysfunction. Kidney biopsy showed a glomerular and tubulo-interstitial nephropathy by oxalate deposits. Genetic testing was used to confirm histopathological evaluation, demonstrating the c.731T>C mutation at exon 7 of AGTX gene.

Conclusions: This case of PH type 1 was peculiar for the clinical presentation (renal failure without evidence of urolithiasis or nephrocalcinosis) and for the glomerular histopathological aspect of oxalate deposition. To our knowledge, this is the first demonstration of CaOx deposition in the glomeruli to be reported in the literature. The histopathological diagnosis enable us to study in deep the bio-humoral profile of the patient and to reach an accurate diagnosis.

Introduction

Hyperoxaluria may be either inherited or acquired. Primary Hyperoxaluria (PH) is a rare autosomal recessive disease characterized by increased endogenous oxalate production and accumulation in renal and extrarenal tissues. PH has three defined subtype. Type 1 (PH1), the most common type of PH, is caused by a deficiency of the liver enzyme Alanine/Glyoxylate Aminotransferase (AGT) which results in metabolic overproduction of oxalate and glycolate. In PH type 2 (PH2), deficiency of Glyoxylate Reductase/Hydroxypyruvate dehydrogenase (GRHPR) results in metabolic overproduction of oxalate and glycerate. Primary Hyperoxaluria of type 3 (PH3) is caused by mutations in the HOGA1 gene that reduce function of the mitochondrial enzyme 4-Hydroxy-2-Oxoglutarate Aldolase (HOGA1) [1]. Secondary hyperoxaluria are usually a consequence of gastrointestinal diseases frequently associated with fat malabsorption: inflammatory bowel diseases, cystic fibrosis, bariatric surgery or short bowel syndrome [2] or increased dietary intake of oxalate [3]. Oxalate does not seem toxic to hepatocytes, but since it cannot be metabolized in mammals, it can only be filtered at glomerular level and also secreted by renal tubules with urinary excretion levels >0.5 mmol/1.73 m^2 per day in PH patients [4]. Owing to the high urinary oxalate excretion, the urine become supersaturated for calcium oxalate (CaOx) resulting in crystals formation within the tubular lumen [5]. In all forms, the oxalate excess is excreted in the urine and frequently patients with PH present signs or symptoms related to kidney stones and progressive nephrocalcinosis. Renal dysfunction ensues with accumulation of oxalate excess within the parenchyma that induces interstitial inflammation and fibrosis that result in progressive loss of renal function [6]. Here we present a case of a young man with an unexplained progressive renal failure.

Case Report

A 19 year old man went to the emergency because of an asthma attack. Blood analyses revealed renal failure and for this reason he was admitted to our Unit. On admission, the patient showed a blood pressure of 130/70 mmHg, no other particular physical findings were seen. Laboratory data were as follows: serum creatinine 1.98 mg/dl,

Blood Urea Nitrogen (BUN) 11.20 mmol/l, Glomerular Filtration Rate (GFR) 42 ml/min/1.73 m, WBC 8.99 × 10.9/L, RBC 4.88 × 10.12/L, hemoglobin 14.7 g/dL, platelet count 182 × 10.9/L, Na 141 mmol/L, K 4.0 mmol/L, Cl 108 mmol/L, Ca 2.32 mmol/L, proteinuria was absent, urinary sediment showed microhematuria, and rare crystals of calcium oxalate. Immunological screening for glomerulonephritis (complement, immunoglobulins and auto antibodies) and other blood data were mostly within the normal range. Familial and medical history was essentially negative. Renal ultrasound evidenced hyperechoic kidneys of normal size, and with reduced cortico medullary differentiation. Since the patient did not show the presence of kidney stones or nephrocalcinosis, but the laboratory data revealed a renal failure without other specific clinical features, a renal biopsy was mandatory. Moreover, the patient was in good clinical condition on admission to hospital.

Light microscopy on paraffin embedded tissue showed six glomeruli with mild mesangial expansion, normal thickness of capillary basement membranes. In one glomerulus it was possible to observe more mesangial expansion with disappearance of Bowman's space and the presence of birefringent crystals of calcium oxalate. Periglomerular infiltrate and fibrosis were noted (Figure 1). In close proximity of this glomerulus a larger calcium oxalate crystal was revealed at tubular level (Figure 1); interstitial fibrosis associated to mononuclear infiltrate was also observed (Figure 2). Immunofluorescence was negative. The histopathological pictures were suggestive for glomerular and tubulo-interstitial nephropathy by oxalate deposits. It was subsequently assayed

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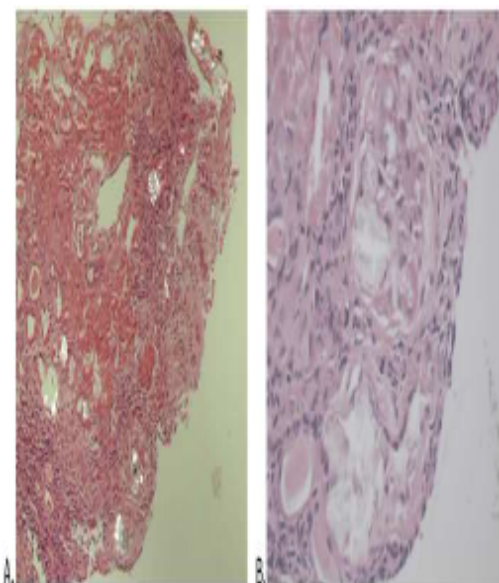
Figure 1: Kidney biopsy with calcium oxalate deposition at glomerular level. Cortical tissue showing a glomerulus with a large birefringent crystalline inclusion consistent with calcium oxalate. The same crystalline inclusion is present at tubular level where it is possible to note the loss of cellular borders, sloughing of cells into lumen (H&E A. 200X and B. 400X original magnification).
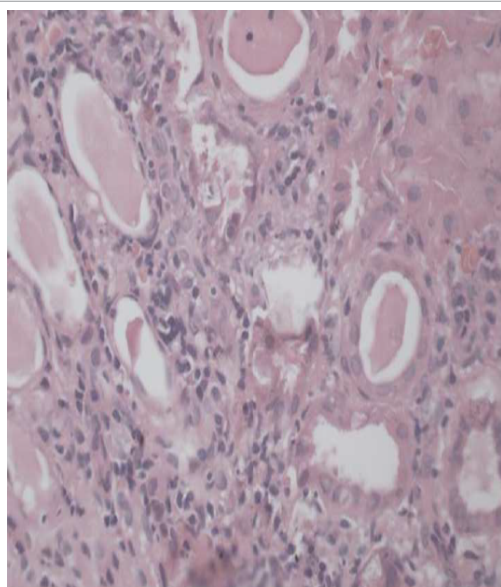

Figure 2: Interstitial involvement in kidney biopsy. Interstitial fibrosis associated to mononuclear infiltrate and dilated tubules (H&E original magnification 400X).

the dosage of urinary organic acids that evidenced an hight excretion of oxalic, glycolic acids and trace of glycerol. To confirm the diagnosis of hyperoxaluria type 1 molecular analysis of AGXT gene was made, after obtaining written informed consent, and revealed the presence of c.731T>C mutation at exon 7 in homozygosis which determines the replacement of isoleucine 244 with a threonine. This mutation is unlikely to cause complete lack of protein production [7]. The patient was discharged with a diagnosis of PH Type 1 and treated with water care, sodium citrate (6 g die) and pyridoxine (600 mg die) therapy. The patient was not compliant to the clinical follow-up suggested and it was difficult to monitor urinary oxalate levels changes. After 7 months from

the diagnosis, renal ultrasound revealed for the first time the presence of spots with shadow back at pyramids level. This finding was confirmed by CT (Computed Tomography) that evidenced soft rib hyperdense to the cortico-medullary passage. Within two years, the patient was in End Stage Renal Disease (ESRD) and he was on dialysis three times a week.

Discussion

Kidney damage in PH has already been described [4]. CaOx salts are poorly soluble in body fluids and calcium oxalate deposits are observed within renal tissue as nephrocalcinosis or nephrolithiasis. This leads to progressive renal injury, inflammation and tubular obstruction resulting in interstitial fibrosis, kidney failure and ESRD. CaOx crystals interact with the renal tubule epithelium and are deposited into the renal interstitium where they induce strong inflammatory response, sometimes with the formation of "foreign-body" type granulomas, and progressive interstitial fibrosis. Recently Cartery et al., [8] described in kidney biopsies of patients with acute oxalate nephropathy, the presence of glomerulosclerosis in addition to known tubular damages. The case-report presented is peculiar either for the atipycal onset of the disease (nor nephrolithiasis nor nephrocalcinosis but renal failure) and for the evidence in kidney biopsy of crystals at glomerular level (Figure 1). To our knowledge there are not in literature other demonstrations of CaOx deposition in glomeruli. When glomerular filtration rate (GFR) decrease (30-40 ml/min) renal capacity to excrete calcium oxalate is significantly impaired, and is possible to observe deposition in extra renal tissues (systemic oxalosis). Oxalosis may involve different organs as myocardium, bones and bone marrow.

Moreover, renal histopathology in patients with crystal deposits due to secondary hyperoxaluria showed tubular atrophy and interstitial fibrosis ranged from mild to moderate and did not track closely with glomerular sclerosis [9]. Progressive renal parenchyma inflammation and interstitial fibrosis due to nephrocalcinosis and recurrent urolithiasis cause renal impairment, which usually progress to ESRD. Renal failure secondary to crystal nephropathy has generally attributed to intratubular obstruction but recently some Authors [10] have demonstrated that Nalp3-null mice (nucleotide-binding domain, leucine-rich repeat inflammasome) are completely protected from progressive renal impairment and mortality due to oxalate nephropathy as compared with wild type mice, emphasizing the role of the inflammasome. Upon activation NALP3 proteins recruit the protease caspase-1 that cleaves the biologically inactive precursors of IL-1β and IL-18 to generate their mature inflammatory counterparts. There are evidence that hyperoxaluria is able to induce apoptotic changes in renal tubular epithelial cells involving TNF and FAS patways [11]. Since 1994 it has been known that renal cells exposure to calcium oxalate crystals results in activation of many different patways, gene expression changes and initiation of DNA synthesis in epithelial cells [12]. This mechanism likely occurs in the tubulointerstitial compartment, but what happen at glomerular level?

In our case the first sign of oxalosis was kidney failure without evidence of nephrocalcinosis or urolithiasis. Although stone formation is often observed in the urinary tract, the detection of crystal deposition in renal biopsy specimens is relatively rare, because renal biopsy might be avoided in case of urinary tract stones. In our patient renal biopsy examination was performed to clarify renal dysfunction. Intriguing was the discovery of crystals in a glomerulus, but it is difficult to determine which are the pathogenic mechanisms underlying this event. Oxalate is primarily eliminated via renal glomerular filtration and in vitro studies have demonstrated that once adherent to cells, calcium oxalate crystals initiate a cascade of reaction that include crystal internalization, changes

in gene expression, cytoskeletal reorganization and cell proliferation [1]. The presence in our biopsy of birefringent crystals of calcium oxalate in glomeruli and the discovery of inflammatory cells both at interstitial and periglomerular level suggest us that both mechanical and inflammatory process could be responsible of ESRD.

Were there special conditions in our patient which favored crystals aggregation in glomeruli? May the mutation found have played a role in this histopathological aspect? It is difficult to demonstrate a genotype-phenotype correlation in PH1 because patients with the same genotype can have different course of the disease. The rarity of the disease and the large number of mutations make it difficult to identify possible genotype-phenotype correlations and factors linked with outcome. The informations reported in the literature focus mainly on two aspects: the age of onset of the disease and the responsiveness to pyridoxine therapy. The presence of the p.Ile244Thr (c.731T>C) mutation seems to be related to a wide range of age at onset and of ESRD [7], in our patient the age of onset was on average and the evolution to the dialysis treatment was relatively fast (two years). The treatment options applied in this case was in accordance with the literature moreover, there was a low response to pyridoxine therapy. This data was in agreement with Fargue who reported in p.Ile244Thr a response to pyridoxine only in few patients [13].

Conclusions

The case described here is peculiar for clinical presentation (renal failure without evidence of urolithiasis or nephrocalcinosis) and for glomerular histopathological aspect of oxalate deposition (Figure 1). To our knowledge, this is the first demonstration of CaOx deposition in a glomerulus to be reported in the literature. We consider important to divulge this rare PH1 phenotype for a better clinical and genetic understanding of the disease.

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