Case Report

Acute renal failure in a middle-aged woman with 2,8-dihydroxyadeninuria

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Introduction

Deficient activity of the enzyme adenine phosphoribosyltransferase (APRT) was first described in 1974 [1]. In the absence of APRT activity, oxidation by xanthine oxidase to 2,8-dihydroxyadenine constitutes the only metabolic pathway for adenine [2]. 2,8-dihydroxyadenine seems to be excreted into the urine by active tubular secretion [3]. The compound is insoluble in urine at the physiological range of pH resulting in crystal formation [2]. However, there are individual differences in the ability to supersaturate the urine with 2,8-dihydroxyadenine [4]. Thus, the clinical spectrum of 2,8-dihydroxyadeninuria runs from an asymptomatic state through brown stains in diapers [5] to renal stones and, in a few cases, renal insufficiency [2,6,7]. About half of the patients are diagnosed in childhood [2]. We report the case of a middle-aged woman, presenting with acute renal failure, in whom 2,8-dihydroxyadeninuria was found.

Case report

The patient is a 55-year-old woman who underwent hysterectomy 12 years ago because of uterine myomatoasis. She has been treated with atenolol for hypertension for 10 years and there is a history of heartburn as well as mild depression. Five years ago, her serum creatinine concentration was 115 μmol/l.

The patient was admitted to the local hospital because of nausea, vomiting, and fatigue of 4 weeks duration. Gastroscopy revealed hiatus hernia and mild distal oesophagitis. This was not considered to be an adequate explanation of her symptoms. On arrival, she was pale and dehydrated. The blood pressure was 120/60 in the supine position but fell to 100/60 on standing. Physical examination was otherwise unremarkable. Laboratory data included haemoglobin 96 g/l, mean corpuscular volume 88.6 fl, white cell count 7.1 × 10⁹/l, platelet count 216 × 10⁹/l, and serum concentrations of sodium 136 mmol/l, potassium 4.1 mmol/l, calcium 2.2 mmol/l, creatinine 1093 μmol/l, urea 37 mmol/l, uric acid 231 μmol/l, and albumin 40 g/l. Urine findings were unremarkable except for a considerable amount of spherical brownish crystals which were recognized as 2,8-dihydroxyadenine crystals (Figure 1). Examined by ultrasound, the kidneys appeared to be of normal size and there were no signs of urinary flow obstruction. To clarify the nature of the renal failure, a kidney biopsy was performed. Approximately 20% of the glomeruli were obsolescent but the others were within normal limits. Extensive crystalline precipitate was seen in tubular lumen and epithelium, especially in the cortex. The crystals were brown on HE staining, birefringent, with a tendency to form globular aggregates within the tubules. Tubular atrophy, interstitial and peritubular fibrosis and patchy interstitial inflammation were seen.

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in connection with the precipitates (Figure 2). Only mild vascular changes with thickening of arteriolar intima and media were noted, consistent with the patients’ history of hypertension.

The diagnosis of 2,8-dihydroxyadeninuria was confirmed by the absence of adenine phosphoribosyltransferase (APRT) activity in erythrocyte lysates. This analysis was performed by the Purine Research Laboratories, Guys Hospital, London, UK.

The patient received symptomatic treatment consisting of hydration and haemodialysis. Moreover, she was given specific treatment for 2,8-dihydroxyadeninuria i.e. a diet, low in purine content, and allopurinol. Her renal function and general condition improved rapidly allowing haemodialysis to be discontinued. She stayed in hospital for 2 weeks. At discharge, her serum creatinine concentration was 617 μmol/l. The renal functional improvement continued over a few months until stabilization at ~ 200 μmol/l. Since treatment was started, 2,8-dihydroxyadenine crystals have only once been observed in the urine.

Discussion

There is little doubt that the acute renal failure (ARF) in this case was caused by 2,8-dihydroxyadenine crystal deposition in renal tubuli. However, ARF was obviously imposed on chronic renal disease as evidenced by increased serum creatinine concentration 5 years before admission and the histopathologic finding of focal glomerulosclerosis and interstitial fibrosis. Regarding the aetiology of the chronic renal insufficiency, we can only speculate about the respective roles of the hypertension and the metabolic disorder.

During the last two decades, ~100 homozygotes of this autosomal recessively inherited disorder of purine metabolism have been found. Most of the reported cases originate from Japan, France, and Iceland [2,5,8,9]. The gene controlling APRT activity is located on chromosome 16 [2]. In Caucasian patients, only type I APRT deficiency has been described, i.e. near total deficiency of APRT activity resulting from one of several known mutations in the APRT gene giving rise to a null allele [2]. About half of the Japanese patients show type II APRT deficiency characterized by decreased in vitro activity of an enzyme form which is probably nonfunctional in vivo [2]. Homozygotes of mutations in the APRT gene manifest 2,8-dihydroxyadeninuria. The reduced enzyme activity in heterozygotes does not have metabolic consequences.

The frequency of heterozygosity for APRT deficiency in several Caucasian populations has been estimated to be 0.4–1.1%, suggesting homozygosity of the order of 1:250 000 to 1:33 000 [2]. These figures far

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Fig. 2. a. Renal cortex demonstrating tubular atrophy, interstitial fibrosis, mild interstitial inflammation and precipitation of crystalline material in tubules (arrows) with giant cell reaction (HE staining, ×170). b. Renal cortex demonstrating birefringent crystalline material in tubular epithelial cells (HE staining, ×420, polarized light).
exceed the reported prevalence, except in Iceland where 16 cases have been found in a population of 270,000 [5]. The high prevalence of 2,8-dihydroxyadeninuria in Iceland can probably be explained both by active search and genetic cluster effect. The figures above indicate that 2,8-dihydroxyadeninuria is generally an underdiagnosed condition, a point that has been emphasized by several authors [8,10]. At diagnosis, most of the reported patients had symptoms in the form of urolithiasis leading to terminal renal failure in a few cases [2,6,7]. Our patient presented with ARF without a history of renal stones. The present case thus confirms the toxic potential of renal 2,8-dihydroxyadenine crystals, which has been indicated by animal experiments [11] and a previously reported paediatric case [6]. The recognition of 2,8-dihydroxyadeninuria is important due to the simple and effective treatment that is available. Moreover, the diagnosis is easily made by routine microscopic investigation of urine. However, the diagnosis is easily overlooked if the microscopist is not familiar with the typical structure of the 2,8-dihydroxyadenine crystals (Figure 1) or misses the brownish colour of the urine sediment of many of these patients [5]. The identity of the crystals can be confirmed by ultraviolet and infrared spectrophotometry but analysis of APRT enzyme activity constitutes the ultimate diagnostic procedure.

The aim of the treatment is to reduce the concentration of 2,8-dihydroxyadenine in the urine. This can be achieved by ample fluid intake, a diet deficient in purine content and inhibition of the activity of xanthine oxidase by allopurinol. The recommended dose of allopurinol is 5–10 mg/kg daily, adjusted according to renal function [12] and disappearance of urinary crystals [2]. It should be pointed out that alkalization of the urine is of no benefit. Care should be taken when giving blood transfusions containing adenine as a preservative, a precaution that also applies to known heterozygotes.

In summary, 2,8-dihydroxyadeninuria is probably an underdiagnosed cause of renal stones and renal failure, the latter emphasized by the present case. The diagnosis of this condition is easily made by routine microscopic investigation of urine and treatment is effective if renal damage has not progressed too far at diagnosis. Therefore, we recommend that urine microscopists should be trained to recognize the typical 2,8-dihydroxyadenine crystals.

References

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