KIDNEY BIOPSY TEACHING CASES

Decreased Kidney Function and Crystal Deposition in the Tubules After Kidney Transplant

Piero Stratta, MD,[1] Giovanni Battista Fogazzi, MD,[2] Caterina Canavese, MD,[1] Andrea Airoldi, MD,[1] Roberta Fenoglio, MD,[1] Cristina Bozzola, MD,[3] Irène Ceballos-Picot, PharmD, PhD,[4] Guillaume Bollée, MD,[5] and Michel Daudon, PharmD, PhD[6]

Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive purine enzyme defect that results in the inability to utilize adenine, which consequently is oxidized by xanthine dehydrogenase to 2,8-dihydroxyadenine (2,8-DHA), an extremely insoluble substance eventually leading to crystalluria, nephrolithiasis, and kidney injury. We describe a case of APRT deficiency not diagnosed until the evaluation of a poorly functioning kidney transplant in a 67-year-old white woman. After the transplant, there was delayed transplant function, urine specimens showed crystals with unusual appearance, and the transplant biopsy specimen showed intratubular obstruction by crystals identified as 2,8-DHA using infrared spectroscopy. APRT enzymatic activity was undetectable in red blood cell lysates, and analysis of the *APRT* gene showed 1 heterozygous sequence variant, a duplication of T at position 1832. The patient was treated with allopurinol, 300 mg/d, and transplant function progressively normalized. Because patients with undiagnosed APRT deficiency who undergo kidney transplant may risk losing the transplant because of an otherwise treatable disease, increased physician awareness may hasten the diagnosis and limit the morbidity associated with this disease.
Am J Kidney Dis 56:585-590.

INDEX WORDS: Adenine phosphoribosyltransferase (APRT) deficiency; crystal nephropathy; renal biopsy; renal transplant; crystalluria; urinary sediment.

Around the world, registries still report an unacceptably high prevalence of undiagnosed causes of end-stage kidney failure, ranging from 15% to >50%. It is likely that genetically determined chronic kidney disease accounts for a large fraction of these cases.[1-3] Obviously, undiagnosed kidney disease in native kidneys negatively affects the chances of having a successful kidney transplant, and such failures are even more difficult to accept in the case of undetected, but treatable, diseases. We describe the case of a kidney transplant recipient with a metabolic deficiency that was not diagnosed until the evaluation of a poorly functioning transplant.

CASE REPORT

Clinical History and Initial Laboratory Data

A 67-year-old white woman underwent transplant of a kidney from a 73-year-old deceased donor in December 2007. From childhood, the patient had experienced repeated renal colic with recurrent episodes of spontaneous elimination of small kidney stones, which never were examined. Family history was negative except for hypertension. Chronic kidney disease of unknown cause with small kidneys was diagnosed when she was 63 years old during an evaluation for hypertension, and maintenance dialysis therapy for end-stage renal disease attributed to nephroangiosclerosis was started 2 years later.

Donor kidney biopsies performed at the time of transplant showed a normal parenchymal pattern with mild interstitial and vascular damage. After transplant, there was delayed transplant function, with serum creatinine level never decreasing to <3.5 mg/dL (<309 μmol/L; estimated glomerular filtration rate [eGFR], 13.9 mL/min/1.73 m^2 [0.23 mL/s/1.73 m^2] assessed using the 4-variable Modification of Diet in

From the [1]Department of Clinical and Experimental Medicine, Nephrology and Transplantation and International Research Centre Autoimmune Disease (IRCAD), Maggiore Hospital of Novara; [2]Research Laboratory on Urine, Nephrology Unit, Fondazione IRCCS, Ospedale Maggiore-Policlinico, Mangiagalli e Regina Elena, Milano; [3]Department of Medical Science Section Pathology of the Amedeo Avogadro University, Maggiore Hospital of Novara; and Departments of [4]Metabolic Biochemistry B, [5]dult Nephrology, and [6]Biochemistry A, Necker-Enfants Malades Hospital and Paris Descartes University, Paris, France.

Received May 20, 2009. Accepted in revised form December 15, 2009. Originally published online as doi:10.1053/j.ajkd.2009.12.028 on March 22, 2010.

Address correspondence to Piero Stratta, MD, Nephrology and Transplantation, Department of Clinical and Experimental Medicine, & International Research Centre Autoimmune Disease (IRCAD) of the Amedeo Avogadro University, Novara, Ospedale Maggiore della Carità, Corso Mazzini 18 28100 Novara, Italy. E-mail: strattanefro@hotmail.com or piero.stratta@unipmn.it

0272-6386/10/5603-0021$36.00/0
doi:10.1053/j.ajkd.2009.12.028

Renal Disease [MDRD] Study equation) and a subsequent further increase in serum creatinine level to 5 mg/dL (442 μmol/L; eGFR, 9.2 mL/min/1.73 m^2 [0.15 mL/s/1.73 m^2]). Kidney ultrasound was normal, and urine specimens showed specific density of 1.015, pH 6, trace protein and hemoglobin, rare red blood cells, and a few crystals lacking diagnostic features.

Kidney Biopsy

Transplant kidney biopsy performed 3 weeks after surgery showed normal glomerular, interstitial, and vascular morphologic patterns, but intratubular obstruction by crystals of unknown type. These crystals were absent in the initial donor biopsy specimens; von Kossa stain was negative, indicating the absence of phosphate. Despite aggressive intravenous fluid administration and use of furosemide, transplant function did not improve. A second transplant kidney biopsy therefore was performed 2 weeks later, again showing many brown and irregular needle-shaped intratubular crystals (Fig 1A) that were refractile when examined under polarized light (Fig 1B).

Diagnosis

The final diagnosis of acute kidney injury caused by intratubular obstruction by 2,8-dihydroxyadenine (2,8-DHA) crystals was rendered after crystal analysis, quantitative enzymatic assay for adenine phosphoribosyltransferase (APRT) activity in erythrocytes, and analysis of the *APRT* gene.

Crystal Analysis

Repeated examination of the urinary sediment using phase contrast microscopy showed the presence of unusual crystals. Some crystals appeared as round particles with dark edges, whereas others had an irregular shape and size. Moreover, although some crystals were free in urine, isolated or in clusters, others were embedded within the matrix of casts, a finding that unequivocally showed their tubular origin. Using polarized light, the crystals showed a strong polychromatic birefringence (Fig 2). Phase contrast investigation gave conflicting results. The round particles (Fig 2A) might have been identified as 2,8-DHA crystals, but this possibility was ruled out because of their birefringence (Fig 2B) and the lack of "Maltese cross" appearance typical of 2,8-DHA crystals.

The definitive confirmation that the crystals were composed of 2,8-DHA came from results of infrared spectroscopy performed on a sample of filtered and dried urine sediment and a fragment of tissue from the kidney biopsy specimen. These findings are consistent with previous studies that have shown that 2,8-DHA crystals may have unusual morphologic features, especially in patients with impaired kidney function.[4-6]

Determination of APRT Enzymatic Activity

APRT enzymatic activity was measured in red blood cell lysates using radiolabeled ^{14}C-adenine in a chromatographic assay as described previously.[7,8] This assay showed no detectable activity.

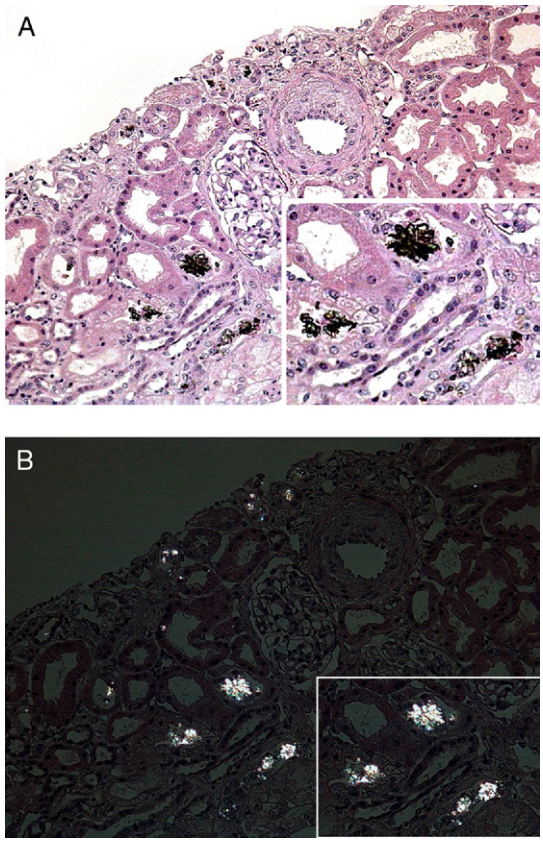

Figure 1. Light microscopy of the kidney transplant biopsy specimen. (A) Cortical tissue includes a glomerulus, middle-sized artery, and several tubules. Round brown crystals are visible in tubular cells and occlude the tubular lumen (original magnification, ×200). Inset, higher magnification shows the needle-shaped features of the crystals (original magnification, ×400). (B) The same tissue area under polarized light (original magnification, ×200). The crystals (at higher magnification in the inset) are birefringent (original magnification, ×400).

Genetic Analysis

Genetic analysis was performed after written informed consent was obtained from the patient. All coding regions and intron/exon junctions of the *APRT* gene were amplified using polymerase chain reaction from genomic DNA and sequenced directly using the polymerase chain reaction primers (full information, including primer sequences, is provided in Item S1, provided as online supplementary material available with this article at www.ajkd.org). Sequences were compared with the theoretical sequence of the *APRT* gene using Serial Cloner software (Serial Basics, serialbasics.free.fr), with GenBank accession number NG_008013.1 used as the sequence reference, except that numbering is based on the A of the initiation codon being position 1.

This analysis showed only 1 heterozygous sequence variant, a duplication of T at position 1832 in the genomic DNA. This position is the second nucleotide of intervening se-