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Case Report

A Case Report of 2,8-Dihydroxyadenine Nephropathy after Kidney Transplantation: what we Have Done and what we have to do

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Abstract

Adenine Phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of the purine metabolism which results in the conversion of adenine into 2,8 Dihydroxyadenine (DHA) due to the activity of the xanthine Oxidoreductase (XOR). Patients affected by APRT deficiency if not treated with inhibitors of XOR may develop 2,8- DHA nephropathy that in turn might progress to End-Stage Kidney Disease (ESKD) with the need of kidney transplant. The high rate of misdiagnosis of 2,8-DHA nephropathy in native kidneys could lead to the failure of kidney graft in transplanted patients affected by APRT deficiency. Here, we report the case of a 61-years old patient with ESKD due to misdiagnosed 2,8-DHA nephropathy who underwent kidney transplantation and developed an early recurrence of 2,8-DHA nephropathy in the graft successfully treated with steroids, hydration, XOR-inhibitors and hemodiafiltration. In our knowledge this is the first time that a hemodiafiltration has be used in combination to steroids and XOR-inhibitors in the treatment of a 2,8- DHA nephropathy recurrence in kidney graft.

Keywords: 2,8-DHA nephropathy; Adenine Phosphoribosyltransferase (APRT) deficiency; Case report; Hemodiafiltration; Kidney transplant

List of Abbreviations: APRT: Adenine Phosphoribosyltransferase; CKD: Chronic Kidney Disease; CMV: Cytomegalovirus; DHA: Adenine Into 2,8 Dihydroxyadenine; DHAN: 2,8-DHA Nephropathy; ESKD: End-Stage Kidney Disease; HDF: Hemodiafiltration; MPA: Mycophenolic Acid; sCr: Serum Creatinine ; TCMR: T Cell-Mediated Rejection; XOR: Xanthine Oxidoreductase

Introduction

Adenine Phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of the purine metabolism which results in the conversion of adenine into 2,8 Dihydroxyadenine (DHA) by the activity of the xanthine Oxidoreductase (XOR). The DHA is highly insoluble in urine at physiological pH so it precipitates causing kidney stones and crystals that aggregate in the tubular lumen, tubular epithelial cells and interstitium, leading to tubular-interstitial inflammation and fibrosis [1,2]. Consequently, patients affected by APRT deficiency may develop chronic Kidney Disease (CKD) in a percentage of 15-20%. A prompt diagnosis of APRT deficiency based on DHA crystals in urine together with the absence/reduction of APRT enzyme activity in erythrocytes allows setting the appropriate treatment with XOR-inhibitors [3,4]. Nevertheless, the diagnosis of APRT deficiency is often delayed and frequently performed when CKD is already developed or, even worse, after kidney transplantation. Indeed, recurrence of 2,8-DHA Nephropathy (DHAN) affecting kidney graft determines acute graft dysfunction or even graft loss [5]. Here, we report a case of recurrence of DHAN in a kidney transplant patient and the treatment that we adopted to rescue the graft.

Case Presentation

A 61-years old Caucasian man with ESKD of unknown origin on regular hemodialysis treatment from February 2020 underwent kidney transplantation in 2021. In childhood the patient experienced frequent renal colic with kidney stones treated with pyelotomy. At that time, the radiotrasparency of the calculi have led to hypothesize that the calculi were composed of uric acid without performing chemical analysis of them. In addition, the patient has never been treated with XOR-inhibitors given the normal levels of serum uric acids. In May 2021, he underwent kidney transplantation in our hospital from a deceased death brain donor. Immunosuppression included basiliximab, tacrolimus, Mycophenolic Acid (MPA) and steroids with an immediate recovery of graft function reaching the Serum Creatinine (sCr) value of 3.8 mg/dl on postoperative day 12. Due to a rising of the creatinine value to 4.4 mg/dl in the subsequent days, an allograft biopsy was performed. The histological examination revealed a borderline acute T Cell-Mediated Rejection (TCMR) and intratubular crystals in the renal cortex. The crystals were reddish brown tinged in hematoxylin and eosin stain and were birefringent under polarized light. These crystals, unlike oxalate stones that are colorless, showed light blue staining on trichrome and appeared black on silver stain. The biopsy findings strongly support the hypothesis of DHA crystals (Figure 1).

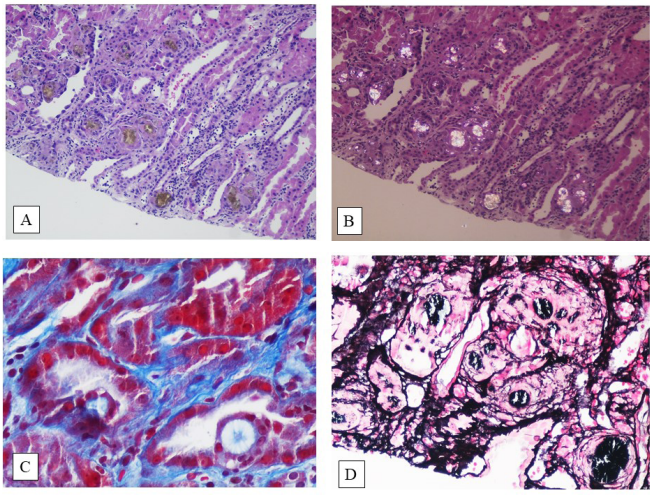

Figure 1: Pathological findings in renal biopsy, (**A**) a lower view shows intraluminal tubular reddish brown crystals (H&E, x 100); (**B**) the same field as in A is shown under polarized light and crystals are birefringent (H&E, x 100); (**C**) the crystals are light blue on trichrome stain (x400); (**D**) the crystals are black on silver stain (x200).

Based on the histological data, we performed a urine analysis searching for purine metabolites using liquid chromatography-mass spectrometry revealing a high concentration of adenine supporting the hypothesis of APRT deficiency. In addition, the APRT deficiency was confirmed by the reduction of APRT activity in erythrocytes lysate using high performance liquid chromatography analysis [4,6]. Consistently, an accurate urine analysis was performed according to Manoni et al [7] allowing to identify the yellow-brown crystals of DHA (Figure 2). Sanger sequencing analysis of APRT gene showed homozygosity for the known pathogenic variant c.400+2dup (dbSNP: rs745594160), which is the most common variant of APRT gene in Europe (allele frequency between 0.18% and 0.043%) [8].

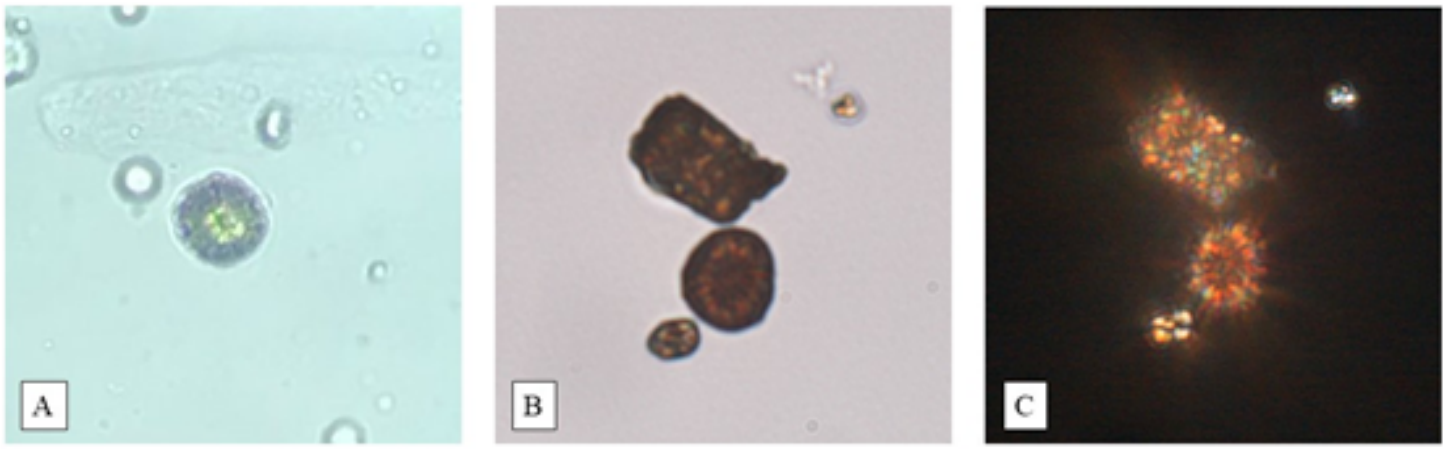

Figure 2: **(A)** Urinary sediment showing spherical brownish crystal with a birefringent and pseudo-Maltese cross appearance by optical microscopy in standardized chamber; (**B**) Polarized light view allows to identified the yellow-brown crystals of 2,8-DHA; (**C**) crystalluria study by phase contrast microscopy revealing typical 2,8-DHA crystals appearing round and reddish-brown with characteristic central Maltese cross pattern.

Due to the diagnosis of DHAN, the histological presence of borderline TCMR was reviewed considering that DHAN per se could be associated with the presence of inflammatory cells in tubules and in the interstitium caused by the interaction between crystals and tubular cells. For this reason, we promptly treated the patient with boli of methylprednisolone and we started allopurinol 300 mg/die to reduce the amount of plasma DHA. Prior to XOR-inhibitors therapy, the serum level of uric acid was 6.5 mg/dl with a urinary excretion of 0.33 mg/die. In addition, based on our experience on kidney transplant in patients with ESKD caused by hyperoxaluria type I, we treated the patient with five consecutive Hemodiafiltration (HDF) sessions to promptly remove the serum DHA avoiding their precipitation in the graft while waiting for the lowering effect of allopurinol. HDF treatments were performed without ultrafiltration and with a generous amount of intravenous hydration. At discharge, the sCr was 2.4 mg/dl, uric acid 2.2 mg/dl and urinary uric acid 0.12 mg/die (Figure 3).

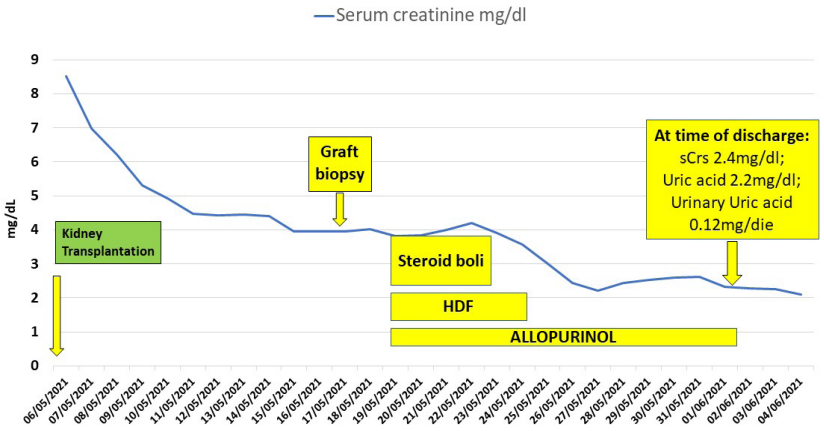

Figure 3: Evolution of serum creatinine from transplantation to the discharge including the treatments administrated on the basis of the diagnosis of 2,8-DHA nephropathy performed with allograft biopsy.

After discharging, the patient experienced a urinary bacterial infection and Cytomegalovirus (CMV) infection successfully treated with antibiotics and valganciclovir, respectively. One month after kidney transplantation sCr rose to 3.5 mg/dl and a graft biopsy was carried out. The histological findings confirmed the presence of DHA crystals slightly increased compared to the previous biopsy along with interstitial inflammation and tubulitis. Thus, we increased the daily dose of steroid to prednisone 25 mg/die enhancing anti-inflammatory effect while reducing MPA to 180/bid, in order to avoid the risk of over immunosuppression considering the recent replication of CMV DNA. At the same time, a switch from allopurinol 300 mg/die to febuxostat 80 mg/die was performed.

At present, the patient is doing well, the graft function is stable with a sCr of 1.9-2.2 mg/dl without significant presence of DHA crystals in the urine.

Discussion and Conclusions

APRT deficiency is a rare autosomal recessive hereditary disease of the purine metabolism. Typically, the disease is associated to the presence of urolithiasis and/or crystalline nephropathy due to the lack of activity of APRT which cause the precipitation and deposition in the kidneys of 2,8-DHA crystals [9]. Based on the incidence of APRT gene heterozygosis mutations in Japan and in Europe, the estimated prevalence of the disease in homozygosity is 1:50.000-1:100.000. Thus, the few cases of DHAN recorded suggest that the disorder is underdiagnosed. Consistently, the age at diagnosis varies from childhood to oldness and in rare cases it remains misdiagnosed and untreated even when patients developed ESKD. In these cases, DHAN can recur in transplanted kidney with the risk to develop allograft dysfunction and graft loss. On the other hand, the early diagnosis of APRT deficiency based on the stone analysis or by the crystals identification in the urine and the start of XOR-inhibitors therapy could prevent the development or the progression of CKD due to DHAN and the recurrence in transplanted patients. The case here described of early develop of DHAN soon after transplantation in a patient listed for kidney transplant without a previously diagnosis of APRT deficiency, highlights the misdiagnosis of the disease. In addition, the rescue therapy adopted soon after the diagnosis of graft dysfunction due to DHAN, included for the first time at our knowledge HDF treatments for rapid removal of serum DHA while waiting for the reduction of DHA production induced by XOR-inhibitor. It is known that a recurrence of DHAN after kidney transplantation could be associated with acute graft dysfunction caused by the huge amount of DHA crystals previously accumulated in the body that are rapidly excreted in the urine by the graft with a high risk of tubular crystals precipitation [10]. At our knowledge 2,8-DHA has a molecular weight of 167.13 g/mol that means 167.13 Daltons as reported by https://pubchem.ncbi.nlm.nih.gov/compound/92268. Thus, we speculated that HDF might contribute to the removal of plasma 2,8-DHA. Due to the removal of oxypurinol, the active metabolite of allopurinol with HDF, an additional dose of allopurinol after dialysis treatment should be consider. Based on the presence of inflammatory cells in tubules and in the interstitium together with DHA crystals demonstrated in the allograft biopsy, we decided to treat the patient with steroid boli. Nevertheless, in our case a differential diagnosis between a borderline TCMR and an inflammatory infiltration of the tubules and interstitium was a hard issue to perform.

Infact, in this setting it is possible to observe an acute tubular injury due to crystals incorporation into the tubular epithelial layer by endocytosis or encapsulation. This process induces atrophy and/or rupture of the tubular basement membrane and consequently the deposition of crystals into the interstitial compartment with an inflammatory response [11]. Recently, Klinkhammer et al [12] using a mice model of DHAN demonstrated that a tubular reparative process namely extratubulation induced by medium-sized DHA crystals incorporated in the tubular epithelial cells in coordination with machrophages might translocate crystals in the interstium leading to granulomatous inflammation. They also demonstrated that knockout mice for the Tnfr1 gene that encodes for the TNF receptor 1, TNFR1, is associated with a better prognosis of DHAN through the reduction of CD44 and annexin 2 expression on tubular cells. Taken together these data may help in the future to distinguish a borderline rejection from a tubular-interstitial inflammation by the detection of macrophages in the graft tissue of kidney-transplanted patients with recurrence of DHAN.

Recently, a study by Runolfsdottir et al. [13] demonstrated that the treatment with XOR inhibitors administered prior transplantation in patients with ESKD due to DHAN, reduces the recurrence of DHAN in the graft to 27% compared to the recurrence rate of 75% in untreated patients [14]. Nevertheless, a prompt initiation of XOR inhibitor and steroid therapies could be effective to ameliorate the outcome of DHAN recurrence in kidney graft in patients without a previously diagnosis on native kidneys [15]. In conclusion, our case report indicates that hemodiafiltration in addition to therapy with steroids, hydration and XOR- inhibithors is effective for the treatment of early recurrence of 2, 8 DHA nephropathy in kidney graft. Indeed, hemodiafiltration contributes to a rapid removal of plasma 2,8-DHA giving time to allopurinol to reduce the 2,8-DHA production. However, in order to avoid a recurrence of 2, 8 DHA nephropathy after kidney transplantation, kidney transplant centers should consider a urine analysis to find out 2,8-DHA crystals if a urine output is already present, or testing the APRT enzyme activity in red cell lysate in patients with unexplained renal failure associated with history of urolithiasis prior to list them for transplantation. It is also advisable to enquire about consanguinity in the parents of the patients in consideration of the autosomal recessive inheritance pattern.

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