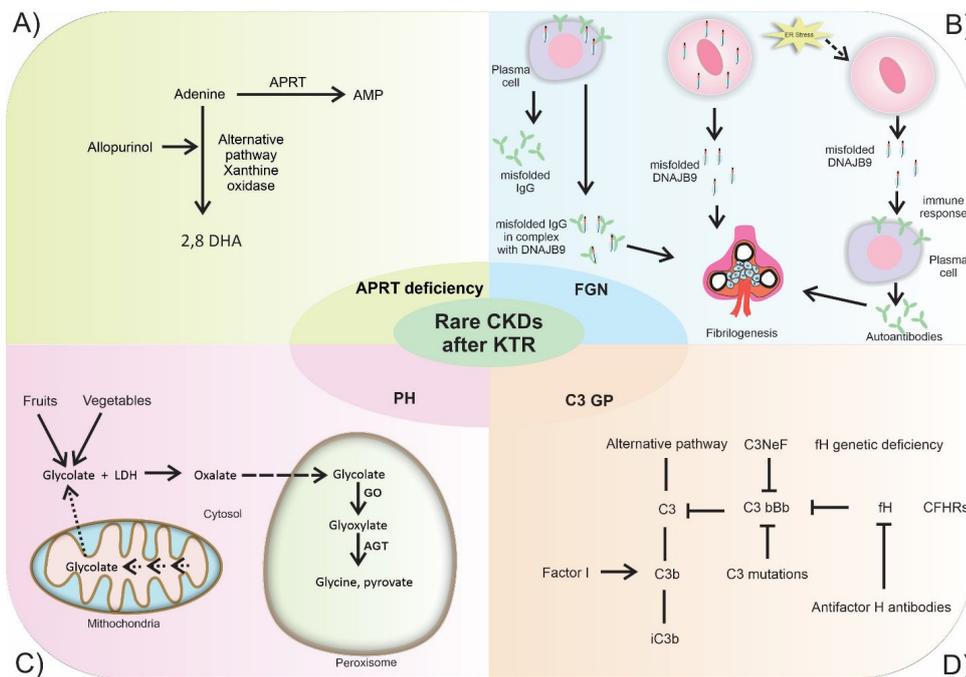


## Recurrence of rare disease after kidney transplant

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### Graphical abstract



Molecular mechanisms of rare chronic kidney diseases including adenine phosphoribosyl transferase (APRT) (A), fibrillary glomerulonephritis (FGN) (B), primary hyperoxaluria (PH) (C), and C3 glomerulopathy (C3 GP) (D). 2,8 DHA: 2,8 dihydroxyadenine, AGT: Alanine glyoxylate aminotransferase, AMP: Adenosine monophosphate, APRT: Adenine phosphoribosyl transferase, C3 GP: C3 glomerulopathy, C3NeF: C3 nephritic factor, CFHRs: Complement factor H related proteins, DNAJB9: DnaJ homolog subfamily B member 9, fH: factor H, PH1: primary hyperoxaluria type 1.

### Implication for health policy/practice/research/medical education:

Although kidney transplantation (KTx) is the standard gold therapy for end-stage renal disease (ESRD), this treatment is not a definitive and complete approach for kinds of rare chronic kidney disease (CKD) such as primary hyperoxaluria (PH), adenine phosphoribosyl transferase (APRT), C3 glomerulopathy (C3 GP), and fibrillary glomerulonephritis (FGN). These diseases frequently recur after kidney transplant, expect FGN mimic acute rejection. For this reason, monitoring of such rare diseases is necessary before KTx, especially in patients with any history of bilateral nephrocalcinosis or nephrolithiasis.

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# Recurrence of rare disease after kidney transplant

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## ABSTRACT

The incidence of chronic kidney diseases (CKDs) by rare etiologies is growing along with other CKDs. This mini-review discusses the epidemiology, pathogenesis, clinical presentation, and diagnosis of rare kidney disease recurrence after kidney transplantation (KTx) including primary hyperoxaluria (PH), adenine phosphoribosyl transferase (APRT), C3 glomerulopathy (C3 GP), and fibrillary glomerulonephritis (FGN). It was shown that PH, like acute rejection, causes delayed graft function, confusing the physicians. Moreover, C3 GP is more prevalent than FGN among kidney transplant patients. Therefore, it is necessary to monitor rare diseases (RDs) before KTx in patients with any history of bilateral nephrocalcinosis or nephrolithiasis.

**Keywords:** Chronic kidney disease, Kidney transplantation, Primary hyperoxaluria, Adenine phosphoribosyl transferase, C3 glomerulopathy, Fibrillary glomerulonephritis

## Introduction

Parallel with the increasing number of chronic kidney diseases (CKDs) in the world, the incidence of CKD by rare etiology is growing. According to recent literature, if the prevalence of a medical condition is less than 50 cases per 100,000 in a year, it is classified as a rare disease (RD) (1). In the nephrology setting, most disorders such as glomerulonephritis or tubulointerstitial disease could be categorized as RDs. At the same time, many RDs could be an essential part of the clinical picture of patients with established end-stage renal disease (ESRD) or rarely diagnosed ones after kidney transplants. According to the main studies, up to 30% of patients with extended ESRD do not have a defined diagnosis of their primary nephropathy (2). From January 2005 to December 2016, a significant number of kidney transplanted patients (25%) have documented RDs [classified according to the Orphanet rare disease nomenclature (ORPHA code)] as underlying CKD. Although kidney transplantation (KTx) is the gold treatment for patients with CKD, this treatment is not a complete strategy for kinds of rare CKD with inherited genetic and enzymatic aberration. Patients with an uncommon genetic disease who received KTx without a correct diagnosis of causal nephropathy could develop unexpected and even rapid allograft dysfunction (3). In this situation, isolated KTx without special preparations is not sufficient for maintaining allograft function. It is not surprising that epidemiological or survival studies about KTx in RDs are still required and most of the accessible studies are defined as case reports/case series studies (4). This mini-review aims to extend some facts about the epidemiology, pathogenesis, clinical management, and diagnosis of some rare but important diseases that could recur after KTx and finally discuss available applied

interventions for decreasing allograft dysfunction in these cases.

## Adenine phosphoribosyl transferase deficiency

Adenine phosphoribosyl transferase (APRT) deficiency is a rare inherited disease with an autosomal recessive pattern that occurs with a prevalence of 1/100,000 in a general population. Mutation in the APRT gene located on chromosome 16 (16q24) in homozygote individuals could result in a complete reduction of the APRT enzyme. This enzyme normally catalyzes the phosphorylation of adenine to soluble adenosine monophosphate. Released adenine from our diet and subsequently phosphorylation of this agent facilitate the elimination of free adenine from the body (5). Due to the complete inactivity of the mentioned enzyme, accumulated adenine is influenced by xanthine oxidase in an alternative pathway and then converted to the 2,8-dihydroxyadenine (DHA) that is accumulated in the body and finally excreted in urine (6). Since the DHA is insoluble in the urine, this agent gradually accumulates in the renal tubes and interstitium and causes DHA nephropathy. Interestingly, extra renal manifestation is rare in this type of enzyme deficiency.

People with APRT deficiency are usually presented with recurrent radiolucent nephrolithiasis without nephrocalcinosis that may be confused with uric acid nephrolithiasis. Depending on nephrolithiasis history, progressive CKD slowly develops in all patients after 20 years but the declining rate of renal function is faster in patients with a history of stone development (7). Literature review has shown that diagnosis is made in about 10% of patients after kidney transplant. Few cases of recurrent 2,8-DHA nephropathy have been reported up to now (6). In this situation, a crystal of 2,8-DHA is only

detectable a few days after transplantation. If diagnosis and treatment begin earlier, prescribing of allopurinol inhibits xanthine oxidase which could decrease the level of 2,8-dihydroxyadenine (6). Although correct diagnosis could improve allograft survival, as a result of the lack of definite clinical and radiological features for this disorder, proper diagnosis is performed with a significant delay (8). Standard analysis of chemical stone structure could not distinguish uric acid stone from DHA crystallopathy or even calcium oxalate because both of them have the same birefringent appearance (6).

Under the polarized light microscopy, 2,8-DHA crystals have the appearance of a round shape and reddish-brown color with a central unique maltose cross structure. Net diagnosis of ARPT deficiency is made by the amount of this enzyme in red blood cells or by using genetic tests. Treatment is based on a low purine diet, proper hydration, and prescribing a low dose of allopurinol (5–10 mg/kg/d) in adults and children (8–10). A timely diagnosis of ARPT deficiency could prevent renal dysfunction and recurrence in KTx. However, difficulty in proper diagnosis results in the probability of recognition in these states and a high index of suspicion is needed including 1- Kidney stone disease resulting in CKD, 2- kidney damage as crystal deposition confirmed by kidney biopsy, 3- History of Reddish-brown diaper in infancy, and 4- Dysfunction in allograft after KTx.

### Primary hyperoxaluria

This heredity RD is produced by the absence of a peroxisomal liver enzyme that converts glyoxylate to glycine named alanine glyoxylate aminotransferase (AGT). The prevalence of this disease is lower than 3 per 1 000 000 (11). In healthy individuals, hydroxyproline firstly is produced in mitochondria from collagen catabolism and then glycolate is produced by the interaction of 4-hydroxy-2-oxoglutarate aldolase (HOGA1) and glyoxylate reductase/hydroxypyruvate reductase. In the second step, glycolate is delivered to the peroxisome and converted to glyoxylate by the glycolate oxidase enzyme. Lastly, the mentioned enzyme (AGT) performs the conversion of glyoxylate to glycine. In the cytosol, glyoxylate could be converted to oxalate by lactate dehydrogenase (LDH). There are three types of primary hyperoxaluria. Primary hyperoxaluria type 1 (PH1) is the most prevalent and severe form of primary hyperoxaluria (PH) resulting from a functional loss of AGT, encoded by the *AGXT* gene which results in the retention of glyoxylate in the cytosol. In a complete deficiency of this enzyme (AGT), glyoxylate is converted to oxalate by the interaction of LDH and results in the accumulation of this product and insoluble calcium oxalate in renal tubules. When the glomerular filtration rate (GFR) is higher than 30 mL/min/1.73 m<sup>2</sup>, most of the symptoms are limited to the kidney and urinary system. The manifestation of renal involvement in adults ranges from asymptomatic nephrolithiasis or recurrent

nephrolithiasis, progressive reduction in kidney function to death from ESRD or due to other complications such as severe sepsis from obstructive urinary tract infection. One registry of patients with an established diagnosis of PH1 has shown that 40% of these patients had ESRD at the time of diagnosis. When GFR is decreased below 30, parallel with decreasing oxalate excretion of urine, systemic retention occurs in other tissues such as bone, eye, skin, and heart named oxalosis that is potentially fatal (12).

In some patients, diagnosis is neglected until its relapses after KTx. Outcomes in these cases are typically very poor and often present with early graft loss. Delayed graft function caused by the deposition of oxalate in allograft is easily misdiagnosed as acute rejection and needs kidney biopsy for accurate diagnosis. For this reason, a high index of suspicion for the diagnosis of PH is very important in patients with CKD and/or ESRD with uncertain etiology especially accomplished with nephrocalcinosis or nephrolithiasis (13). Such patients need exact preoperative screening for PH and proper treatment in both kidneys before KTx (13). Patients with established PH that only receive a kidney transplant have inferior graft survival (14). A recent study in Italy highlights a considerable delay in the diagnosis of post-transplant PH. Consequently, it is recommended for more widespread use of both metabolic and genotyping screening, containing the definite assignment of minor/major allele status among patients with recurrent kidney stones. Thanks to the advances made in medicine, new therapies are accessible which essentially focused on substrate reduction of the oxalate-producing enzymes by using RNA-interference (15). Lumasiran is a new exciting treatment for PH1 that consist of interference RNA which destroys glycolate oxidase mRNAs and consequently decreases the level of glyoxylate and produces oxalate as a main toxic agent in PH1. Studies showed that the use of this drug for six months could normalize the urinary level and decrease the plasma concentration of oxalate in all groups of affected patients independent of age and state of kidney function (12, 16). Lumasiran was approved by the European Medicines Agency for the treatment of hyperoxaluria. Another ongoing enzymatic intervention for decreasing urinary oxalate excretion is the inhibition of the LDH enzyme in the cytosol of the hepatocytes as a drug named stiripentol. This enzyme catalysis the conversion of glycosylate into oxalate. But no case reports are available in this regard (16). When patients with primary hyperoxalosis reach the ESRD, a combination treatment of shortly and high flux hemodialysis and nocturnal peritoneal dialysis could eliminate some of the oxalate from the body. However, the mentioned procedure is not a definitive treatment. After transplantation, plasma levels of oxalate remain high for several months due to the slow excretion of residual oxalate from the body. For this reason, hemodialysis has been frequently used in patients with persistent hyperoxaluria for the prevention of

accumulation of residual oxalate in the kidney. The main target of calcium oxalate gathering is the native kidneys so that subtraction of it could drastically drop total body oxalate levels after transplantation (17).

### C3 glomeropathy

Aberrant regulation of alternative complement pathways results in the aggregation of intense C3 staining with nearly an absence of immunoglobulin in glomeruli named C3 glomerulopathy (C3 GP). Based on data obtained from microscopy, complement studies, and clinical data, this glomerulopathy is divided into three classes: 1 –DDD, 2-C3 glomerulonephritis (GN), and 3-complement factor H-related C3 glomerulopathy (CFHR5 GP). C3 GP essentially involves children and young individuals and may present after an upper respiratory tract infection, especially with streptococcal species. However, predisposition of some people to C3 GP due to the existence of rare variants is well established. Chronic micro hematuria along with having light or heavy proteinuria or not following an infection incidence increases the possibility of C3 GP onset. These glomerulonephritis abnormally activate the complement alternative pathway, the deposit of C3 in the glomeruli, and subsequently, progress renal injury to the ESRD. Fifty percent of patients with these diseases fall into ESRD and some patients have permanent heavy proteinuria that is resistant to the different types of therapies ranging from Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ACEi-ARBs) to immunosuppressive drugs (17). Although C3 GP is an infrequent glomerular disease, it occurs in high rates of patients who are in post KTx period (18). The two largest case series involving 40 patients showed recurrence of disease in 67–84% of patients. In these studies, the median time from a kidney transplant to recurrence was 14–28 months (19). Therefore, post-transplant monitoring and available treatment options are necessary to improve the outcomes of the patients. Patients with C3 GP undergoing KTx and eculizumab treatment experienced the lowest allograft loss related to other therapies such as therapeutic plasma exchange (TPE) and rituximab (81% for rituximab, 42% for TPE, and 33% for eculizumab) (20). In recent case series, a study on 19 patients (12, C3GN; and 7, DDD) showed a high percentage of disease recurrence in both C3GN and DDD, while graft failure was more frequent in DDD (21). The recurrence of CHFR5 GP has been observed in the kidney allograft of patients (22). Although the use of eculizumab for the recurrence of C3 GP residues is controversial, in the absence of other treatments, it can be prescribed for patients with aggravated proteinuria or higher persistent rates of proteinuria that deteriorate kidney function (19).

### Fibrillary glomerulonephritis after KTx

Fibrillary glomerulonephritis (FGN) is one of the scarce glomerular diseases defined by the presence of fibrils in

the glomeruli. Under electron microscopy, fibrils have a random appearance between 12–24 nm diameters. This rare nephropathy usually progresses to kidney failure that requires renal replacement therapy. Currently, a new biomarker has been recognized for FGN by using an anti-rabbit polyclonal antibody and immunohistochemistry named DNAJB9. This biomarker has developed the new gold standard for the diagnosis of FGN with high sensitivity and specificity (23). Because of the difficulty in net diagnosis of FGN specially before DNAJB9 staining as potential mimic of the other glomerulopathies, the rate of recurrence in kidney allograft differs from 8% to 50% among studies (23). But in a recent case –series study, the recurrence rate of 14 confirmed FGN undergoing kidney biopsy and DNAJB9 immunohistochemistry was 21% (3 patients of 14). Despite poor prognosis of FGN in native kidney, the recurrence of this disease in allografts does not significantly affect allograft or patient outcomes. The recurrence of FGN typically had an indolent progression and allograft survival was 67% (24) after 10 years. For this reason, the date of treatment for recurrent FGN in renal allograft is too limited (23).

### Conclusion

Before KTx, all patients with an even minor history of bilateral nephrocalcinosis or nephrolithiasis need to be preoperatively screened for RDs, especially for PH and APRT deficiency. Delayed graft function caused by this RD is simply misdiagnosed as acute rejection and kidney biopsy helps the net diagnosis. Although the C3 GP causes a high rate of recurrence and graft loss after KTx, FGN has a slow course in the KTx.

### Authors' contribution

Conceptualization: FF and MA. Methodology: FF. Validation: FF and MA. Formal analysis: FF and SMH. Investigation: FF and AM. Resources: SMH. Data curation: FF. Writing—original draft preparation: FF, MA and AM. Writing—review and editing: SMH and AM. Visualization: FF. Supervision: MA. Project administration: FF. Funding acquisition: KB.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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