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OPINION REVIEW

Human pegivirus infection after transplant: Is there an impact?

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Abstract

The microbiome's role in transplantation has received growing interest, but the role of virome remains understudied. Pegiviruses are single-stranded positive-sense RNA viruses, historically associated with liver disease, but their pathogenicity is controversial. In the transplantation setting, pegivirus infection does not seem to have a negative impact on the outcomes of solid-organ and hematopoietic stem cell transplant recipients. However, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals. The possible immunomodulatory effect of pegivirus infections remains to be elucidated in further trials.

Key Words: Virome; Human pegivirus; Epidemiology; Solid-organ transplant; Hematopoietic stem cell transplantation

Core Tip: Pegiviruses are single-stranded positive-sense RNA viruses, historically associated with liver disease, but their pathogenicity is controversial. Pegivirus infection does not seem to have a negative impact on the outcome of solid-organ and hematopoietic stem cell transplant recipients. However, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals.

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INTRODUCTION

The microbiome's role in transplantation has received growing interest, but the role of virome remains understudied. Several studies have shown that the virome changes upon immunosuppression initiation[1,2]. Most notable is the increase in the anellovirus but also in pegiviruses.

Pegiviruses are single-stranded positive-sense RNA viruses, most closely related to hepatitis C virus (HCV) in terms of genome organization with structural genes located at the 5' genomic region and non-structural genes at the 3' end[3]. The genome encodes a polyprotein that is co- and post-translationally cleaved into individual viral proteins. Structural proteins common to all pegiviruses are the envelope glycoproteins (E1 and E2), and non-structural proteins are NS2-NS5B[4]. Pegiviruses are classified into eleven species (pegivirus A-K) within the genus *Pegivirus* in the *Flaviviridae* family. Two pegiviruses are known to infect humans, the human pegivirus (HPgV) and the HPgV-2, but their pathogenicity is limited and no clear association with any human disease has been established[5].

HPgV was discovered in 1995 from the sera of patients with hepatitis by two independent investigator groups, who named it GB virus C and hepatitis G virus (HGV), respectively. The HPgV's E2 glycoprotein, involved in the adhesion and fusion with the host cells, targets the production of anti-HPgV antibodies, which appear after the viral clearance and provide partial protection against reinfection[6]. The virus is efficiently transmitted through sexual contact and intravenous substance use, vertically from mother to child, and through exposure to infected blood and blood components[7].

Available data suggest a high prevalence of HpgV viremia (> 40%) in populations with parenteral exposure risk[8]. Although early studies indicated that the HPgV is hepatotropic, numerous subsequent studies have shown that HPgV is rarely detectable in infected individuals' liver tissue. In addition, no evidence of a liver disease potentially linked to HPgV was observed during the follow-up of different patient categories[7].

HPgV-2 was isolated in 2015 from the plasma of HCV-infected patients with multiple blood-borne exposures in the United States[8]. A low prevalence of HPgV-2 viremia has been noted in the general population, but there is an increase in patients with HCV infection and injecting drug users co-infected with HCV[9]. Further studies indicated that HPgV-2 is a lymphotropic but not a hepatotropic virus, which may explain the lack of association with liver disease[10].

HPgVs are distributed globally, and viral RNA is present in roughly 750 million people[6], making it ubiquitous in human populations. The prevalence of HPgV viremia from cross-sectional studies of healthy blood donors in developed countries ranges between 1% and 5%. Nearly 200000 units of HPgVs-contaminated blood products are transfused each year in the United States[11]. In comparison, in developing countries, up to 20% of blood donors have an active infection[12]. Data suggest that approximately 1.5-2.5 billion people are currently infected or have evidence of prior HPgV infection[6].

Numerous studies examined the presence of HPgV in several countries. Generally, a high HPgV prevalence is observed among subjects with parenteral exposure, including those exposed to blood and blood products, those on hemodialysis, those with a history of intravenous substance use, and patients with chronic hepatitis C or human immunodeficiency virus (HIV) infection[13].

HPGV AFTER TRANSPLANTATION OF SOLID ORGANS AND NON-SOLID ORGANS

HPgVs have received much attention due to the possible beneficial immunomodulatory effects by reducing immune activation in patients with other viral diseases such as HIV infection, hepatitis B, and Ebola virus disease[14-17]. On the other hand, HPgV

viremia has also been associated with the development of non-Hodgkin lymphoma (NHL). HPgV is a lymphotropic virus that may cause persistent infection in T and B lymphocytes, reduced Fas-mediated apoptosis, and impaired T cell and interleukin-2 receptor signaling[18]. HPgV infection anticipates the development of NHL by several years and resolved infection was not associated with NHL risk[19]. Pegiviruses have been studied both in hematopoietic stem cell transplantation (HSCT) and solid-organ transplant (SOT) recipients (Table 1).

Studies in HSCT recipients are limited. The prevalence of HPgV in HSCT patients ranges from 18.6%, as described in the study from Switzerland[20], to almost 30% in an earlier French study[21]. As in the general population, the risk of viremia rises with the number of received blood products[20,22]. No significant influence of pegiviruses on HSCT patient outcomes was found. On the other hand, no beneficial effect of pegivirus infections is currently proven; therefore, some studies warrant HPgV donor screening for blood products used in HSCT recipients until more conclusive studies are performed[22].

Early studies in SOT recipients were done mostly in liver transplant (LT) recipients, due to the presumed hepatotropic nature of the virus, all showing a high prevalence but no significant influence on patient outcomes[23-26]. The largest of the studies included in this review is the recent Japanese study on 313 LT recipients. This monocentric study showed an increased prevalence of HPgV in LT recipients compared to hepatectomy controls[27]. As in the earlier studies, there was no significant association between HPgV infection and LT outcomes. The study showed that HPgV infection induced the up-regulation of interferon-stimulated gene (ISG) expression in peripheral blood mononuclear cells[27].

HPgV is transmitted through parenteral, sexual, and perinatal routes[28]. Parenterally exposed individuals such as hemodialysis patients, therefore, have a higher risk of infection. An Indian study using univariate analysis showed that the prevalence of GB virus C/HGV RNA was significantly associated with ≥ 20 hemodialysis sessions[29]. After the transition from dialysis, the prevalence remains high in kidney transplant (KT) recipients, ranging from 12% to 47% in different countries[30-33]. A large Italian study in KT recipients (n = 155) showed an HGV RNA and anti-HGV prevalence of 24% and 17%, respectively[34]. None of the studies above, found any influence on patient outcomes, including kidney or liver function. On the other hand, the largest study in KT recipients (Germany, n = 221)[33] showed that a much higher proportion of KT recipients were exposed to HGV, than that suggested by HGV RNA detection alone. The prevalence of HGV RNA and anti-HGV in the study was 14% and 40%, respectively. Most infected individuals eliminate the virus over time. Unfortunately, the majority of other studies did not include serological analyses. Most of the studies on HPgV were done immediately after the discovery of the virus, focusing mostly on hepatic function or the function of the transplanted organ. Only the most recent study[1] tried to include other post-transplant complications in the analysis, *e.g.*, new-onset diabetes after transplantation or nephrotoxicity in LT recipients. The study highlighted a potential use of anellovirus infection as a proxy for determining the immunological status. At the moment there is no standard way to measure total immunosuppression, besides the widely available through levels of immunosuppressant drugs. In the same study, all of the HPgV positive participants were still alive 5 years after LT, indicating a protective role of HPgV in post-transplantation survival[1].

The paucity of other SOT recipient studies probably reflects the proportionately lower number of those transplants performed. We found no studies evaluating HPgV in simultaneous pancreas-kidney transplantations or lung transplant recipients. The studies in heart transplant recipients are concordant to those in other SOT, showing no adverse outcome but a high HPgV prevalence, up to 36%[35-42].

CONCLUSION

To conclude, pegivirus infection does not seem to have a negative impact on the outcome of transplant recipients. Nevertheless, studies are limited and lacking prospective data. What remains to be elucidated is the possible immunomodulatory effect of pegivirus infections. Also, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals. The subject deserves further research and evaluation.

Table 1 Seroprevalence and RNA prevalence studies in different transplant populations

Type of transplant and period	Country/region	Patients (*n*)	RNA prevalence	Seroprevalence	Comment	Ref.
Liver transplant; 1997-2017	Japan	313	14.1%	/	No significant association between HPgV infection and liver transplant outcomes; HPgV infection induced the up-regulation of ISG expression in peripheral blood mononuclear cells	Izumi *et al*[27], 2019
Renal transplant; 1989-1996	Italy	155	24%	17%	Not associated with disease pathogenicity; Lower serum levels of HCV-RNA in HGV/HCV co-infected carriers compared to those infected with HCV only	De Filippi *et al*[34], 2001
Renal transplant; 2015-2016	Brazil	61	36.1%	/	Most common genotype 2 (80.9%), followed by G3 (9.5%), G1 (4.85), and G5 (4.8%); no significant impact on patient outcomes	Savassi-Ribas *et al*[31], 2020
Renal transplant	France	103 HCV positive RT recipients	28%	/	HGV infection has no detrimental effect on liver enzymes or liver histology in HCV-positive patients	Rostaing *et al*[37], 1999
Heart transplant; 1993-1998	Germany	51 transplant candidates	2.0%; 0	0; 6.0%	RNA persisted after transplant; anti-E2 antibodies persisted after transplant	Kallinowski *et al*[38], 2002
		Post-transplant	36.0% *de novo*	/	RNA persisted in 94% infected patients; No significant correlation between the number of blood transfusions and the infection; No impact on liver disease or patient outcome	
Liver transplant; 1993-1998	Germany	72 transplant candidates	11.%	/	RNA persisted in 88% of infected patients	Kallinowski *et al*[38], 2002
		Post-transplant	36% *de novo*	/	RNA persisted in 87% of infected patients; no significant correlation between the number of blood transfusions and the infection; no impact on liver disease or patient outcome	
Kidney transplant; 1997	Thailand	94	43%	/	Co-circulation of HGV and HCV RNA was detected in 12 patients (13%)	Raengsakulrach *et al*[30], 1997
Heart transplant; 1993-1996	Germany	243	24%	/	HGV infections are transfusion related; not related to the use of mechanical circulatory assist devices or immunosuppression	Wolff *et al*[36], 1996
Liver transplant; 1989-1996	Germany	98	Pre-tx 8.2%; post-tx 44%	/	None of the hepatitis B, hepatitis C, or fulminant hepatitis, were HGV-RNA positive preoperatively; HGV was frequently acquired after LT but had no impact on the short- and medium-term clinical course post-LT	Fischer *et al*[23], 1999
Liver transplant; 2007-2010	Iran	106	9.4%	/	Moderate prevalence of HGV infection in liver transplant recipients	Ebadi *et al*[39], 2011
Kidney transplant; 1986-1990	United States	93	12%	/	HGV infection does not adversely affect clinical outcome during early follow-up	Isaacson *et al*[32], 1999
Liver transplant; 1989-1996	Italy	136	Pre-tx 18.4%; post-tx 47.8%	Pre-tx 26.5%	Liver transplant patients are heavily exposed to HGV before and after transplantation; HGV does not induce liver disease; most infections are self-limited and induce a protective immunity (anti-E2 antibodies presence)	Silini *et al*[40], 1998
HSCT; 1985-1996	France	95	29.5%	/	Acute GVHD, chronic GVHD, or veno-occlusive disease are similar in HGV+ and HGV- recipients in early period after allogenic BMT	Corbi *et al*[21], 1997
Kidney transplant; 1997	Germany	221	14%	40%	The majority of infected individuals eliminate the virus over time	Stark *et al*[33], 1997
Kidney transplant; NA	Turkey	69	42%	/	Genotype 2 is the dominant type; subgroup 2a most common of the isolates	Erensoy *et al*[41], 2002

Liver transplant; 1993-1995	United Kingdom	47	47%	/	HGV does not cause significant liver disease after LT	Karayiannis *et al* [42], 1998
Liver transplant; 1979-1990	Netherlands	39	Pre-tx 15.4%; post-tx 43.6%	/	HGV infection is highly prevalent in liver transplant patients; in the absence of HBV or HCV co-infection with, no long-term negative influence on the graft	Haagsma *et al* [24], 1997
Kidney transplant; 1997-2000	India	70	52.9%	58.6%	GBV-C/HGV RNA significantly associated with ≥ 20 hemodialysis sessions	Abraham *et al* [29], 2003
Liver transplant; 1990-1994	United States	179	Pre-tx 15%; post-tx 50%	/	HGV infection not associated with poor outcome	Hoofnagle *et al* [26], 1997
HSCT; 2011-2017	China	188	18.6%	/	HPgV is highly prevalent in HSCT patients; blood transfusions significantly increase the risk of HPgV infection	Li *et al*[22], 2019
HSCT; 2014-2015	Switzerland	40	35%	/	HPgV is highly prevalent and persists for several months	Vu *et al*[20], 2019

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HGV: Hepatitis G virus; HSCT: Hematopoietic stem cell transplantation; HpgV: Human pegivirus; GBV-C: GB virus C; GVHD: Graft *versus* host disease; BMT: Bone marrow transplantation; ISG: Interferon-stimulated gene.

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CASE REPORT

Diagnosis of acute intermittent porphyria in a renal transplant patient: A case report

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Abstract

BACKGROUND

Acute intermittent porphyria (AIP) is an inherited disorder of porphyrin metabolism with a worldwide distribution and a prevalence ranging from 1 to 9 per million population. AIP is caused by an autosomal dominant-inherited mutation of low penetrance resulting in a deficiency of porphobilinogen deaminase (PBGD) activity. Acute attacks are provoked by stressors such as certain medications, alcohol, and infection. We herein present the first case report of AIP detected in a post-renal transplant patient.

CASE SUMMARY

The patient was a 65-year-old man who underwent transplantation 2 years previously for suspected nephroangiosclerosis and chronic interstitial nephropathy. He subsequently developed diabetes mellitus which required insulin therapy. He had been treated in the recent past with local mesalamine for proctitis. He presented with classic but common symptoms of AIP including intense abdominal pain, hypertension, and anxiety. He had multiple visits to the emergency room over a 6-mo period for these same symptoms before the diagnosis of AIP was entertained. His urinary postprandial blood glucose level was 60 mg/24 h (normal, < 2 mg/24 h). He was placed on a high carbohydrate diet, and his symptoms slowly improved.

CONCLUSION

This case report describes a common presentation of an uncommon disease, in which post-transplant complications and medications may have contributed to precipitating the previously undiagnosed AIP. We hypothesize that the low-

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carbohydrate diet and insulin with which our patient was treated may have led to the attacks of AIP. Alternatively, our patient's mesalamine treatment for proctitis may have led to an acute AIP crisis. A high index of suspicion is needed to consider the diagnosis of a heme synthesis disorder, which presents with the common symptoms of abdominal pain, high blood pressure, and anxiety.

Key Words: Acute intermittent porphyria; Post-transplantation diabetes; Mesalamine; Tacrolimus; Renal transplantation; Case report

Core Tip: This case report describes a common presentation of an uncommon disease, in which post-transplant complications and medications may have contributed to precipitating his previously undiagnosed acute intermittent porphyria. A high index of suspicion is needed to consider the diagnosis of a heme synthesis disorder, which presents with the common symptoms of abdominal pain, high blood pressure, and anxiety in a post-renal transplantation patient.

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INTRODUCTION

Acute intermittent porphyria (AIP) is an inherited disorder of porphyrin metabolism with a worldwide distribution and a prevalence ranging from 1 to 9 per million population with the highest prevalence found in northern Europe[1]. AIP is caused by an autosomal dominant inherited mutation of low penetrance resulting in a deficiency of porphobilinogen deaminase (PBGD) activity[1]. Acute attacks are provoked by stressors such as certain medications, alcohol, and infection. Symptoms include abdominal pain mimicking acute surgical abdomen, sometimes leading to unnecessary laparotomy, as well as neuromuscular and psychiatric disturbances. Late-stage associated conditions include renal insufficiency and hepatocellular cancer[2,3].

We present a patient who underwent deceased donor renal transplantation and subsequently developed AIP. Experience of renal transplantation in patients with AIP is limited. We found three previous reports describing renal transplantation[4,5] or combined liver-renal transplantation[6] in patients with a history of known AIP, but none reporting the diagnosis of AIP in a previously transplanted patient.

CASE PRESENTATION

Chief complaints

Recurrence of abdominal pain, nausea, and vomiting in a kidney transplant patient.

History of present illness

A 65-year-old man reported the appearance of rectal blood in March 2017 and visited a proctologist. He started local mesalamine therapy for proctitis, but the drug was discontinued a few days later due to abdominal pain and constipation. During the subsequent 6 mo, he presented several times to the emergency department complaining of severe abdominal pain, nausea, and vomiting. He related an anxious mood and low energy level in addition to tachycardia and an increase in blood pressure which was no longer well-controlled with his usual therapy. He presented to the emergency room eight times for various complaints (Figure 1): Epigastric pain without mention of mesalamine, agitation and anxiety, thoracic pain, abdominal pain, and precordial pain.

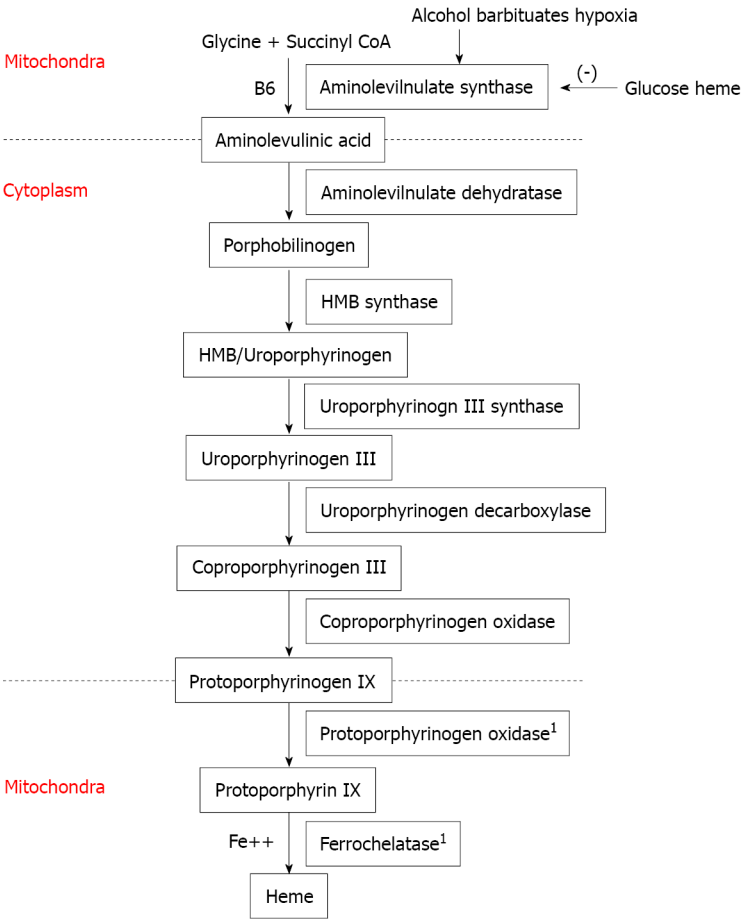

Figure 1 Heme synthesis pathway. [1]Mitochondrial enzyme.

History of past illness

The patient had been treated for hypertension since 1994 and developed ischemic heart disease. His renal function gradually deteriorated over the years due to suspected nephroangiosclerosis and chronic interstitial nephropathy, as ultrasound examination demonstrated small echogenic kidneys. He started hemodialysis in 2008 and was evaluated for renal transplantation; a left nephrectomy was performed for a small incidental renal carcinoma. The histopathologic examination of the nephrectomy specimen revealed angiosclerosis and tubulointerstitial fibrosis. He underwent a deceased-donor kidney transplant in 2015, for which he was treated with tacrolimus, mycophenolate mofetil, and methylprednisolone. He developed diabetes mellitus post-transplant and insulin therapy was initiated (see Table 1).

Personal and family history

The patient had no known family history of porphyria.

Physical examination

The patient was hemodynamically stable with a heart rate of 90 bpm and blood pressure of 160/90 mmHg, but appeared in mild distress. The physical examination revealed an intermittently tender, non-distended abdomen with normal bowel sounds and absent rigidity, rebound, and guarding. The remainder of the physical examination was unremarkable.

Laboratory examinations

Serum levels of hemoglobin, electrolytes, hepatic transaminases, amylase, thyroid function, protein electrophoresis, and C-reactive protein were normal, as was the urine analysis. Renal function was stable with a serum creatinine of 1.2 mg/dL; the urine culture was negative.

Table 1 Medications used

Medication list	Dose	Time
Tacrolimus	0.5 mg; 0.5 mg	08:00; 20:00
Mycophenolate mofetil	1000 mg; 500 mg	08:00; 20:00
Methylprednisolone	2 mg	08:00
Aspirin	100 mg	13:00
Ranitidine	300 mg	08:00
Cinacalcet	30 mg	08:00
Bisoprolol	5 mg	08:00
Amlodipine	10 mg	20:00
Nitroglycerin TTS	10 mcg	1 d
Atorvastatin	40 mg	20:00
Calcitriol	0.25 mcg	08:00
Na bicarbonate	1000 mg qd	
Insulin		
Bromazepam	2.5 mg/mL 5 drops bid	

TTS: Transdermal therapeutic system.

Imaging examinations

Plain X-rays of the abdomen showed distended colon and fecal impaction, and ultrasound revealed that the liver, spleen, pancreas, and transplanted kidney were of normal size and consistency and that the site of the left nephrectomy was occupied by intestinal loops.

FINAL DIAGNOSIS

Based on the clinical symptoms and the radiologic and laboratory findings, a diagnosis of porphyria was attained. The level of postprandial blood glucose (PBG) in a 24-h urine sample was determined utilizing spectrophotometric technique (ClinRep for the porphyrins and ClinEasy for PBG; RECIPE Chemicals and Instruments, Munich, Germany). The level of PBG was significantly elevated to - 60 mg/24 h in the first sample (normal value, < 2 mg/24 h), whereas the values for porphyrins and coproporphyrins were negative, supporting the hypothesis of AIP (Figure 2).

TREATMENT

After AIP was confirmed, treatment was initiated with a carbohydrate-rich diet, and the patient's symptoms slowly improved. The timeline of events is listed in Figure 1.

The patient was referred to the genetics division for analysis of the PBGD (also known as the hydroxymethylbilane synthase) gene and also splicing variants using sequencing and polymerase chain reaction amplification, but tested negative for the most common available single nucleotide polymorphisms (SNPs). It is notable that the patient's insulin requirements did not change after the high-carb diet was started; his insulin doses, glycated hemoglobin, and glucose levels did not change.

OUTCOME AND FOLLOW-UP

The patient's symptoms slowly improved with a carbohydrate-rich diet.

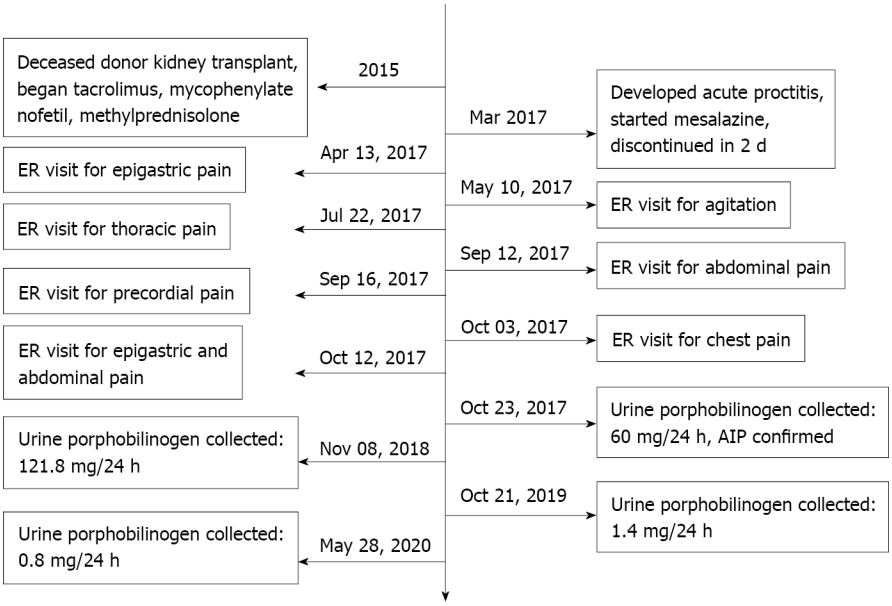

Figure 2 Timeline of patient symptoms and response to treatment. ER: Emergency room; AIP: Acute intermittent porphyria.

DISCUSSION

To our knowledge, this is the first report of new onset AIP symptomatology in a renal transplant patient. We hypothesize that our patient had pre-existing but undetected AIP, and that he may have a genetic predisposition due to his European ancestry. Although Lazareth *et al*[7] have reported improved AIP outcomes following renal transplantation, the hepatic origin of the disease may present a risk of acute attack in case of post-transplant complications, medications, infection, or reduced carbohydrate intake.

As mentioned in the History of Past Illness section, the nephrectomy specimen, in addition to the small renal carcinoma, revealed chronic tubulointerstitial lesions and nephroangiosclerosis. According to Pallet *et al*[8], in a large cohort of patients with porphyria-associated kidney disease, kidney biopsies revealed "diffuse glomerulosclerosis and chronic interstitial changes", and thus it is conceivable that the AIP was responsible for the renal insufficiency in the native kidneys. On the other hand, these findings are very common and nonspecific in nephropathy patients, and may not accurately reflect the etiology of the renal disease.

Over 500 PBGD mutations have been described in AIP. Penetrance is incomplete, and less than 10 per cent of individuals with each genetic defect may have phenotypic expression of the disease[9]. The enzyme deficiency alone is not sufficient to trigger crises; environmental factors are required. Thus, 80%-90% of those with the enzyme deficiency never manifest symptoms[10]. Acute attacks are often precipitated by drugs such as barbiturates and other anticonvulsants, calcium channel blockers, sedatives, antibiotics, hormones, alcohol, tobacco, calorie-restricted or low carbohydrate diets, infection, surgery, psychological disorders, or other comorbid conditions. In some patients, no precipitating stressor is found[11].

The diagnosis of acute porphyria is challenging - symptoms are not specific and may mimic various digestive and neuropsychiatric diseases. Very intense, diffuse abdominal pain is often the earliest characteristic symptom. Nausea, vomiting, constipation, urinary retention, arrhythmias, labile blood pressure, and hyponatremia may coincide with the pain[11]. The AIP crisis may also have associated neurological complications such as respiratory arrest due to bulbar involvement, quadriplegia, neuropathic limb pain, depression, and suicide[12]. In the present case, the patient presented with the principal signs and symptoms of AIP: Very intense abdominal pain, hypertension, and anxiety/depression disorder.

The clinical criteria for AIP diagnosis include the paroxysmal nature of the symptoms, while the biochemical criteria include a more than fivefold increase in urinary porphobilinogen excretion, which is also elevated in 88% of AIP patients in remission. DNA analysis of the *PBGD* gene is the most reliable diagnostic method.

Current treatment options include heme preparations during an acute attack; intravenous glucose 10% alone (see discussion below) - at least 300 g daily - may

resolve mild attacks or may be given while waiting for heme arginate to be available. During acute attacks, correction of dehydration and electrolyte imbalances as well as monitoring of vital capacity and expiratory flow rate is important. This patient responded to a high complex carbohydrate diet. No variation of the immunosuppressive protocol has been required.

A high prevalence of AIP among the Spanish population has been reported, and variations on the CYP2D6 enzyme, important for hepatic drug metabolism, in this population may impact the penetrance of this disorder in those with a PBGD enzyme mutation[13]. Additionally, G6PD deficiency is common among Mediterranean populations[14], and the levels of G6PD can affect AIP exacerbations[15]. Although our patient tested negative for the most common SNPs, with over 500 mutations identified affecting the *PBGD* gene[16]which can cause AIP, it is possible that our patient had a rarer or undescribed mutation.

Aminolaevulinic acid synthase is the first enzyme in the heme synthesis pathway (see Figure 2 for details of the heme synthesis pathway) and is regulated by glucose and heme, such that high levels of glucose inhibit heme synthesis and prevent attacks of AIP. Although AIP is caused by a defect in the third enzyme of the heme synthesis pathway (PBGD), stimulation of aminolevulinate synthase by decreased glucose leads to activation of the heme synthesis pathway and causes an acute attack of AIP. Increased glucose, including glucose infusions and avoidance of fasting between attacks, has been shown to be beneficial in the management of AIP[17]. The American Porphyria Foundation suggests a 55%-60% carb-based diet for patients with AIP and cautions against fasting or crash-dieting[18]. This patient recovered upon being placed on a high-carb diet, supporting the hypothesis that a low-glucose state triggered his attack.

It is possible that the patient's diabetes combined with his low carbohydrate intake resulted in low uptake of glucose into the cells, mimicking the fasting state known to trigger AIP attacks[11]. Post-transplant diabetes is commonly induced by tacrolimus treatment through decreased insulin secretion, increased insulin resistance, and beta-islet cell toxicity[19]. A case report of a patient with hereditary coproporphyria showed that high levels of tacrolimus triggered an acute attack and that the patient's symptoms resolved once tacrolimus levels were lowered into the therapeutic range, thereby suggesting a role for tacrolimus in precipitation of AIP attacks[20].On the other hand, hyperinsulinism may be associated with clinically stable AIP[21].

Mouse models of AIP show key differences in glucose metabolism between AIP and non-AIP mice. There are also differences in the level of enzymes in the pentose-phosphate pathway and glutathione metabolism, which can lead to decreased hepatic glucose and exacerbate AIP. AIP mice have been shown to rely more on gluconeogenesis and fatty acid metabolism for maintaining blood glucose levels as compared to control mice, which rely more on glycogen metabolism[22].

Although medications are a common trigger for AIP, the patient was not taking any medications commonly known to cause AIP. He was transiently treated with mesalamine, although the Norwegian Porphyria Center website[23],which serves as a clearinghouse for information on drug "porphyrinogenicity", indicates that mesalamine has low porphyrinogenic potential. In addition, the patient's symptoms continued several months after stopping the drug. The patient had not been exposed to other new drugs, had not undergone surgery, and had no recent infections during this time, rendering this etiology less likely.

CONCLUSION

We present an older subject with a common presentation of an uncommon disease, whose post-transplant complications and medications may have contributed to precipitating his previously undiagnosed AIP. A high index of suspicion is needed to consider the possibility of a heme synthesis disorder, which presents with the common symptoms of abdominal pain, high blood pressure, and anxiety, in renal transplant patients.

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CASE REPORT

Is *de novo* membranous nephropathy suggestive of alloimmunity in renal transplantation? A case report

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Abstract

BACKGROUND

Post-transplant nephrotic syndrome (PTNS) in a renal allograft carries a 48% to 77% risk of graft failure at 5 years if proteinuria persists. PTNS can be due to either recurrence of native renal disease or *de novo* glomerular disease. Its prognosis depends upon the underlying pathophysiology. We describe a case of post-transplant membranous nephropathy (MN) that developed 3 mo after kidney transplant. The patient was properly evaluated for pathophysiology, which helped in the management of the case.

CASE SUMMARY

This 22-year-old patient had chronic pyelonephritis. He received a living donor kidney, and human leukocyte antigen-DR (HLA-DR) mismatching was zero. PTNS was discovered at the follow-up visit 3 mo after the transplant. Graft histopathology was suggestive of MN. In the past antibody-mediated rejection (ABMR) might have been misinterpreted as *de novo* MN due to the lack of technologies available to make an accurate diagnosis. Some researchers have observed that HLA-DR is present on podocytes causing an anti-DR antibody deposition and development of *de novo* MN. They also reported poor prognosis in their series. Here, we excluded the secondary causes of MN. Immunohistochemistry

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was suggestive of IgG1 deposits that favoured the diagnosis of *de novo* MN. The patient responded well to an increase in the dose of tacrolimus and angiotensin converting enzyme inhibitor.

CONCLUSION
Exposure of hidden antigens on the podocytes in allografts may have led to subepithelial antibody deposition causing *de novo* MN.

Key Words: Post-transplant nephrotic syndrome; Recurrent membranous nephropathy; Secondary membranous nephropathy; Alloimmunity; Cryptic antigens; Case report

Core Tip: This is a case presentation of a patient who developed post-transplant nephrotic syndrome 3 mo after transplantation and was diagnosed with *de novo* membranous nephropathy (MN). He had received a well-matched living donor kidney. According to the literature, the most common causes of *de novo* MN include secondary causes and antibody mediated injury, which we ruled out. This patient was treated with increased dosage of tacrolimus and an angiotensin converting enzyme inhibitor, which resulted in a good recovery. We favoured a new concept of pathogenesis of *de novo* MN, which requires the identification of the causative antigens.

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INTRODUCTION

The development of proteinuria after kidney transplantation is not uncommon, with 3% to 14% of recipients presenting with post-transplant nephrotic syndrome (PTNS). The risk of allograft loss with persistent proteinuria at 5 years is around 48% to 77% [1]. This may be due to either a recurrence or new (*de novo*) development of glomerular disease. It is rather difficult to differentiate between these two possibilities because only 15% to 20% of native kidneys are subjected to biopsy before transplantation[2]. Factors, such as immunosuppression, donor specific anti-human leukocyte antigen (HLA) antibodies (DSA), acute rejection, hypertension and infection, might pose a diagnostic dilemma in regard to the clinical picture and histopathology of the graft. We hereby present a case of a kidney transplant patient who developed PTNS in the early period following transplantation.

CASE PRESENTATION

Chief complaints

There were no chief complaints. Abnormal signs were observed at the 3-mo follow-up after renal transplantation.

History of present illness

A 22-year-old male patient was diagnosed with end-stage kidney disease due to chronic pyelonephritis and received dialysis for 8 mo. He received a live donor kidney transplant from his 42-year-old mother in August 2020. HLA-A, B and DR mismatches were 1-1-0. He was not given induction therapy and was maintained on triple immunosuppression (tacrolimus, mycophenolate mofetil and prednisolone). He was discharged on day 7 with a serum creatinine of 0.9 mg/dL (normal: 0.7-1.2 mg/dL). His graft duplex scan was normal, and tacrolimus 12-h trough level was maintained at 10 ng/mL. At the time of discharge, his urine protein was normal. At the 3-mo follow-

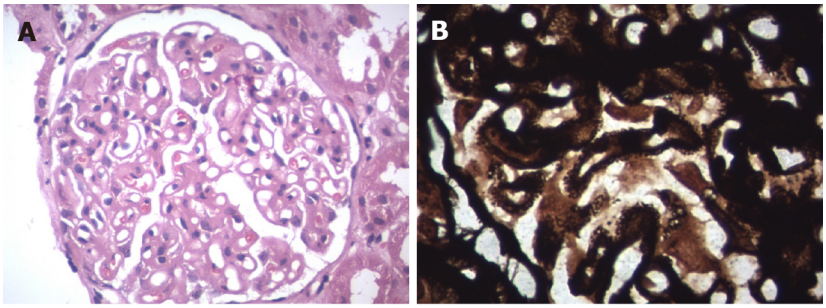

Figure 1 Light microscopy. A: Haematoxylin and eosin staining (40 × magnification) showed diffuse thickening of the glomerular basement membrane; B: Periodic acid-Schiff silver methenamine stain (100 × magnification) showed membrane thickening.

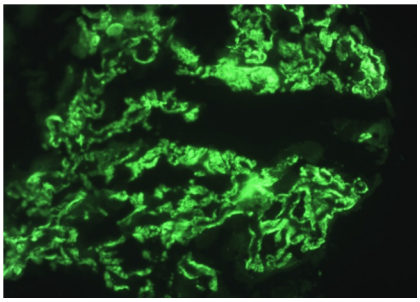

Figure 2 Immunofluorescence microscopy showed granular IgG deposits in the glomerular basement membrane.

up, he had signs of mild pedal oedema.

History of past illness

The patient had a history of end-stage kidney disease due to chronic pyelonephritis treated with a renal transplantation 3 mo prior. A bilateral ureteric re-implantation for vesicoureteral reflux had been performed at the age of 6 years.

Personal and family history

No significant personal and family history.

Physical examination

We observed mild pedal oedema, which was pitting in nature.

Laboratory examinations

His urine showed + 4 proteinuria, and urine protein/creatinine ratio was 4.6 mg/mg (normal: < 0.2 mg/mg) with stable serum creatinine. We recorded a serum albumin level of 3 gm/dL and total cholesterol of 295 mg/dL, suggestive of PTNS.

Imaging examinations

Allograft biopsy was performed and subjected to light, immunofluorescence and electron microscopy to rule out secondary causes of PTNS. Light microscopy revealed a thickening of the basement membrane and spikes at high power magnification with periodic acid-Schiff silver methenamine stain (Figures 1A and 1B). Immunofluorescence microscopy showed IgG deposits along the glomerular basement membrane in a granular pattern (Figure 2), suggesting membranous nephropathy (MN).

EVALUATION AND DIFFERENTIAL DIAGNOSIS

This was a case of PTNS that was histologically suggestive of MN. We conducted further investigations to identify secondary causes of MN, antibody-mediated rejection (ABMR), and differentiation of recurrence *vs de novo* MN.

This patient's serology was negative for hepatitis B virus, hepatitis C virus and hepatitis E virus. Cytomegalovirus was also undetected by polymerase chain reaction.

Antiphospholipase A2 receptor antibody testing was negative. There was no evidence of post-transplant malignancy upon clinical assessment and detailed investigations. Secondary causes of MN were ruled out.

In this recipient, the donor class II HLA was fully matched. When he developed proteinuria, DSA was negative. His biopsy did not show any changes of ABMR. Electron microscopy did not show duplication of peritubular capillaries or glomerular basement membrane (Figure 3). The C4d stain was also negative (Figure 4). These findings ruled out ABMR in our case.

The biopsy revealed positive IgG1 deposits and scarcity of IgG4 after immunohistochemistry (Figures 5A and 5B).

FINAL DIAGNOSIS

Post kidney transplant *de novo* MN.

TREATMENT

The patient's tacrolimus 12-h trough level at the time of development of PTNS was 5.9 ng/mL. The dose of tacrolimus was increased to achieve a level of 9-12 ng/mL. Ramipril was commenced and optimized to 5 mg twice a day. Serum creatinine and potassium were checked on day 10 and remained unchanged. The dose of ramipril was kept tolerable to avoid hypotension.

OUTCOME AND FOLLOW-UP

At 6 mo after the biopsy, his urine protein creatinine ratio decreased to 0.6 mg/mg. His graft function remained stable with a serum creatinine level of 0.94 mg/dL.

DISCUSSION

Recurrence of idiopathic MN after renal transplant is seen in 25%-40% of cases. A diagnosis of *de novo* MN is reported in 1%-2% of post-transplant adults and up to 9% in paediatric renal transplant recipients[3]. The exact incidence is difficult to ascertain due to variability in pretransplant biopsies to confirm diagnosis[2,4].

New onset hepatitis virus infection, particularly hepatitis C virus and hepatitis B virus, is a common secondary cause of *de novo* MN[2,3,5]. Taton *et al*[5] reported a probable association of hepatitis E virus infection with post renal transplant *de novo* MN. Teixeira *et al*[6] reported a case of cytomegalovirus infection and its relationship to *de novo* MN. Risk factors such as post-transplant malignancy, ureteral obstruction and renal infarction have also been found to cause *de novo* MN[2]. Prasad *et al*[7] reported a case of *de novo* MN in a patient having Alport's syndrome as a native kidney disease. It has been reported that *de novo* MN is more common in patients with IgA nephropathy[2,3,7]. We ruled out all the secondary causes of MN in our patient.

Sometimes, a recurrence of MN may be misdiagnosed as *de novo* MN due to undiagnosed native kidney disease[2,4]. Pathology findings of *de novo* MN are like those of idiopathic MN, except for mesangial proliferation, focal and segmental distribution of subepithelial deposits, and simultaneous presence of different stages of disease in *de novo* MN[3]. Anti-phospholipase A2 receptor antibodies have been identified in most cases of idiopathic MN, whereas anti-phospholipase A2 receptor antibodies are absent in *de novo* MN because of other causative antigens that remain unidentified[2,3,8-10]. Different IgG subtype depositions have been reported in cases of primary/recurrent MN and *de novo* MN. IgG4 was commonly deposited in recurrent MN, whereas IgG1 was observed in *de novo* MN. In our case, there was an absence of anti-phospholipase A2 receptor antibodies and IgG1 deposition in the kidney biopsy, which confirmed the diagnosis of *de novo* MN.

Schwarz *et al*[11] published a retrospective observational study of renal transplant subjects transplanted between 1970 and 1992 who developed *de novo* MN. They observed histopathological features of acute vascular rejection in 17 out of 21 recipients and interstitial rejection in 12 out of 21 recipients. During this period, the

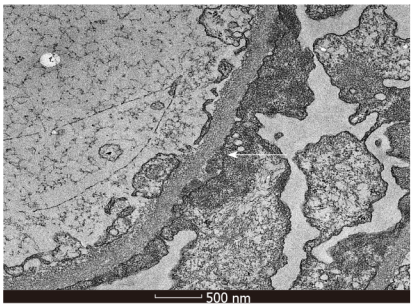

Figure 3 Electron microscopy showed subepithelial electron dense deposits (× 13500).

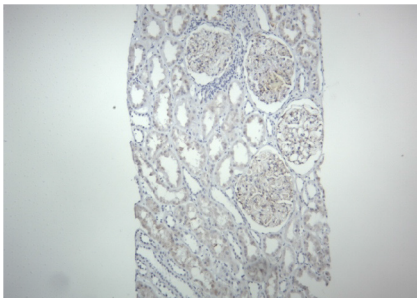

Figure 4 Immunohistochemistry (10 × magnification) was negative for C4d stain.

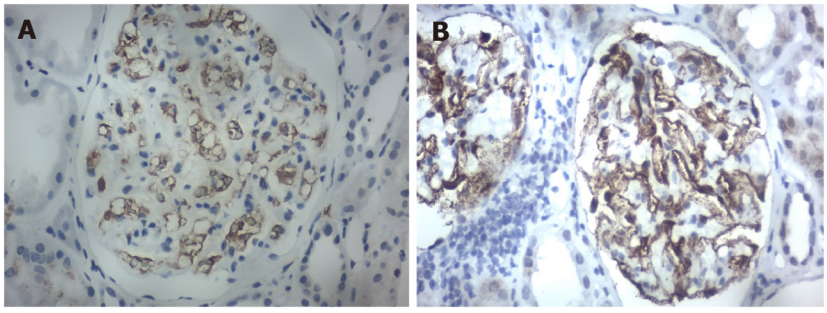

Figure 5 Immunohistochemistry staining (40 × magnification). A: IgG4 was negative; B: IgG1 was positive.

availability of DSA measurement techniques and knowledge of diagnosing ABMR may have been limited. Other investigators have reported a possible relationship of donor-specific alloantibodies in the development of *de novo* MN[12]. Wen *et al*[13] reported the presence of HLA-DR on podocytes of recipients who developed *de novo* MN; they also reported a higher incidence of peritubular capillaritis, intimal arteritis and C4d deposits in post-transplant MN in comparison to recurrence of idiopathic MN in the renal allograft. There are also reports of poor prognoses in patients who had *de novo* MN possibly related to ABMR[11,12]. Interestingly, Bansal *et al*[14] reported a case of *de novo* MN following a renal transplant between conjoined twins. Even in our case, the mother was the donor, with fully matching HLA-DR. The biopsy of our patient confirmed that there were no changes suggestive of acute or chronic ABMR.

There may be another pathophysiological mechanism precipitating in the development of *de novo* MN. It is likely that immunological, viral, mechanical or ischemic injury to the graft may expose the podocyte cryptic antigens to the recipient immune system. This may trigger an activation of innate immunity, resulting in production of auto- or alloantibodies against the antigens on the podocyte. This antigen-antibody complex develops at subepithelial sites and causes activation of complement and membrane injury[9].

There is lack of consensus in the published literature about the optimal management of *de novo* MN. Schwarz *et al*[11] reported no response to methylprednisolone bolus and a high graft loss. El Kossi *et al*[12] hypothesized that *de novo* MN was an atypical manifestation of ABMR. If a secondary cause, such as viral infection or malignancy, is

identified, then the treatment of the underlying cause might treat MN. Cyclophosphamide or rituximab has been tried, as in the treatment of idiopathic MN[8]. In our case, we optimized the dose of tacrolimus and started an angiotensin converting enzyme inhibitor; the proteinuria was significantly reduced, and graft function was stable after 6 mo, suggesting a good prognosis.

CONCLUSION

De novo MN, a rare disease in renal allografts, may be due to exposure of a hidden antigen on the podocytes that is recognized by the immune system of the recipient. The causative antigens still need to be identified. The reported poor prognosis of *de novo* MN may be due to misdiagnosed ABMR, as it was in an era prior to routine availability of DSA by the Luminex platform (Bio-Rad Laboratories, Hercules, CA, United States) and recognition of C4d for an ABMR diagnosis. Proper evaluation and targeting of the pathophysiological processes may help in the management of these patients.

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