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Four Cases of Kidney Transplants With Donor HCV-Derived Immune Complex Glomerulonephritis

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Received 30 January 2024; revised 25 March 2024; accepted 1 April 2024; published online 5 April 2024

Kidney Int Rep (2024) **9,** 1903–1907; https://doi.org/10.1016/j.ekir.2024.04.010
KEYWORDS: direct-acting antivirals; donor-derived glomerulonephritis; HCV-positive donor; kidney donor pool; kidney transplant outcome

INTRODUCTION

Although outcomes from hepatitis C virus (HCV)-positive and HCV-negative donor kidneys are comparable in the short term, questions remain about the clinical consequences of preexisting HCV-related kidney injury, which may go undetected at the time of organ procurement.[1-5] We previously reported a case of successful kidney transplantation from an HCV-positive donor with mesangial proliferative glomerulonephritis (GN) into an HCV-negative recipient with reversal of HCV-associated histologic changes after antiviral treatment.[6] Here, we present an additional 4 cases of recipients of HCV-positive kidneys with preexisting HCV-associated immune complex–mediated GN (ICGN), of whom 2 had evidence of reversal of the pathologic finding on a follow-up biopsy following treatment with direct-acting antivirals.

RESULTS

A summary of donor, recipient and transplant characteristics, and clinical course for the cases are presented in Supplementary Methods/Table 1 and Supplementary Figure S1, respectively.

Recipient A1 (from donor A) had end-stage kidney disease attributed to chronic calcineurin inhibitor toxicity after a dual lung transplant whose post–kidney transplantation course was complicated by hypovolemic shock and delayed graft function. The postreperfusion biopsy showed acute tubular injury, and minimally active ICGN with membranoproliferative features and IgM-dominant deposits, with 2+ IgM staining accompanied by isointense light chain staining (Figure 1a and b). On postoperative day 2, the recipient was noted to have an HCV viral load of 28 IU/ml. Sofosbuvir-velpatasvir was initiated and he became aviremic on postoperative day 22. Allograft biopsy for an increase in serum creatinine (SCr) level on postoperative day 20 demonstrated unchanged ICGN. Urinalysis showed 78 red blood cells and 300 mg/dl protein. Approximately 1 year after the transplant, he underwent another biopsy for assessment of acute kidney injury which showed ICGN with only trace staining for IgM, along with acute T cell–mediated rejection. Electron microscopy was notable for segmental duplication of basement membranes as well as mild mesangial matrix accumulation. Urinalysis was positive for 29 red blood cells with urinary protein-to-creatinine ratio of 700 mg/g. He subsequently received corticosteroid therapy, with SCr improving to 1.3 mg/dl. The recipient ultimately died from septic shock as a complication of metastatic adenocarcinoma approximately 3 years after transplant. A biopsy performed 3 years posttransplant due to an increase in SCr in the setting of sepsis demonstrated negative immunofluorescence studies, consistent with the resolution of donor-derived HCV-related ICGN along with evidence of pyelonephritis. Urinary albumin-to-creatinine ratio (UACR) at that time had decreased to 78 μg/mg from 1500 μg/mg a year earlier.

Table 1. Summary of donor, recipient, and transplant characteristics

Donor	A	B	C
Age, yr/sex	53/M	66/M	35/M
Race/ethnicity	Hispanic	Hispanic	Caucasian
Blood type	O	O	B
Height	165 cm	170 cm	183 cm
Weight	64 kg	64 kg	97 kg
BMI	23.5 kg/m^2	22.1 kg/m^2	29.0 kg/m^2
CMV status	Negative	Positive	Negative
HCV status	HCV Ab positive	HCV Ab positive	HCV Ab positive
	HCV NAAT positive	HCV NAAT positive	HCV NAAT positive
HIV status	Negative	Negative	Negative
HBV status	HBsAg negative	HBsAg negative	HBsAg negative
	HBsAb negative	HBsAb positive	HBsAb unknown
	HBcAb negative	HBcAb positive	HBcAb negative
Terminal serum creatinine	1.2 mg/dl	0.8 mg/dl	2.4 mg/dl
Cause of death	Stroke	Motor vehicle accident	Anoxia
Donation after cardiac death	No	No	Yes
Kidney donor profile index	92%	93%	62%

Recipient	A1	A2	B	C
Age, y/sex	60/M	70/M	60/M	50/M
Race/ethnicity	African American	Hispanic	Caucasian	African American
Blood type	O+	O+	O+	B+
Height	188 cm	165 cm	165 cm	188 cm
Weight	73 kg	65 kg	73 kg	75 kg
BMI	20.7 kg/m^2	23.9 kg/m^2	26.8 kg/m^2	21.2 kg/m^2
CMV status	Positive	Positive	Positive	Negative
HCV status	HCV Ab negative	HCV Ab positive	HCV Ab negative	HCV Ab negative
	HCV NAAT negative	HCV NAAT positive	HCV NAAT negative	HCV NAAT negative
HIV status	Negative	Negative	Positive	Negative
HBV status	HBsAg negative	HBsAg negative	HBsAg negative	HBsAg negative
	HbsAb positive	HbsAb positive	HBsAb negative	HBsAb positive
	HBcAb negative	HBcAb positive	HBcAb negative	HBcAb negative
Cause of end-stage kidney disease	Calcineurin inhibitor toxicity	Diabetic nephropathy	Tenofovir toxicity	Focal segmental glomerulosclerosis
HLA mismatch A/B/DR	2/2/1	1/2/0	1/2/2	2/1/1
Donor-specific antibody at time of transplant	No	No	No	No
Cold ischemic time	23 h 9 min	12 h 40 min	28 h 42 min	28 h 49 min
Warm ischemic time	52 min	34 min	37 min	53 min
Nadir serum creatinine	1.2 mg/dl	0.9 mg/dl	2.1 mg/dl	1.1 mg/dl
Delayed graft function	Yes	Yes	No	Yes
Immediate posttransplant complication	hypovolemic shock	None	None	hemorrhagic shock/retroperitoneal hematoma

Ab, antibody; Ag, antigen; BMI, body mass index; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HLA; huma leucocyte antigen; NAAT, nucleic acid amplification test.

Recipient A2 (from donor A) had known chronic HCV infection without evidence of liver cirrhosis pretransplant. He had not received any treatment for chronic HCV before transplant, and the pretransplant peak HCV viral load was >9 million IU/ml with normal liver function tests. The postreperfusion biopsy showed minimally active ICGN with membranoproliferative features and IgM-dominant deposits, with 2+ IgM staining, and mild interstitial fibrosis and tubular atrophy, suggesting that these pathologic changes were donor-derived. HCV viral load was 5,901,324 IU/ml on the day of the transplant. He was initiated on sofosbuvir-velpatasvir on postoperative day 27. The patient became aviremic by week 4 after treatment initiation. The patient's posttransplant course was complicated by delayed graft function, requiring hemodialysis only on postoperative day 1. SCr level subsequently reached a nadir of 0.9 mg/dl with UACR of 851 μg/mg and no red blood cell detected on urinalysis. No additional biopsy was necessary until the last follow-up visit (approximately 3 years and 6 months after transplant) due to the excellent allograft function.

Recipient B (from donor B) had a history of HIV infection and chronic kidney disease stage 5 that was

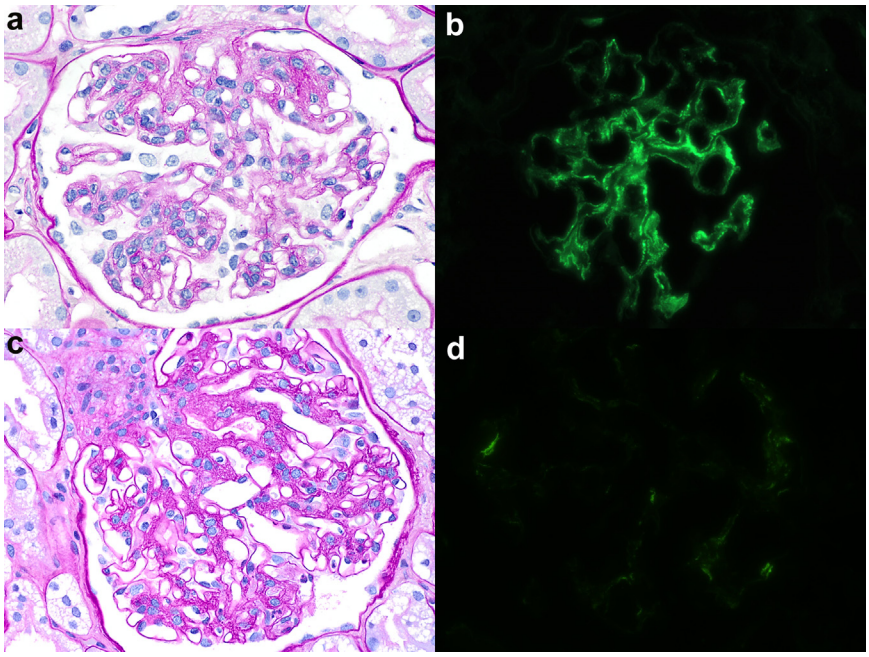

Figure 1. Pathologic features of donor-derived HCV-related immune complex–mediated glomerulonephritis with IgM-dominant deposits. Histologic pattern of HCV-related IgM-ICGN may demonstrate (a, original magnification 600x, periodic acid-Schiff stain) membranoproliferative features with global mesangial matrix expansion and hypercellularity accompanied by glomerular basement membrane duplication (b, original magnification 400x) with granular global mesangial and/or glomerular capillary wall staining for IgM. (c, original magnification 600x, periodic acid-Schiff stain). However, histologic changes of HCV-related IgM-ICGN may be more subtle, with only focal mild mesangial matrix expansion and segmental mesangial hypercellularity. (d, original magnification 400x) Immunofluorescence staining for IgM in cases of HCV-related IgM-ICGN are typically more intense, confluent, and global than minimal IgM staining sometimes present in the normal kidney that are attributed to "entrapping" of IgM. HCV, hepatitis C virus; ICGN, immune complex–mediated glomerulonephritis.

attributed to tenofovir toxicity. At the time of the preemptive transplant, he was on antiretroviral therapy, and his HIV viral load before the transplant was <20 copies/ml, along with a CD4 count of 670 cells/μl. The postreperfusion biopsy showed focal global glomerulosclerosis, mild interstitial fibrosis and tubular atrophy, and minimally active ICGN with mild mesangial expansion, 1+ IgM-dominant deposits, with trace staining for κ, but not λ. After transplant, lamivudine was added to antiretroviral regimen and sofosbuvir-velpatasvir was started for a total of a 12-week course on postoperative day 4. On postoperative day 13, HCV viral load was found to be 2123 IU/ml. Eight weeks thereafter, HCV RNA became undetectable. On postoperative days 39 and 67, biopsies were performed due to allograft dysfunction, and both revealed unchanged minimally active ICGN with urinary protein-to-creatinine ratio of about 300 mg/g with no significant microscopic hematuria on urinalysis at the time of each biopsies. His last SCr level was 2.8 mg/dl with UACR of 342 μg/mg approximately 2 years and 9 months after transplant.

Recipient C (from donor C) had a prior failed kidney transplant due to chronic rejection. Postreperfusion biopsy showed diffuse mesangial proliferative GN (Figure 1c) with 3+ IgM-dominant deposits, accompanied by C3, C1, and isointense light chain staining. He was initiated on a 90-day course of glecaprevir/pibrentasvir on postoperative day 2. HCV viral load was detected on postoperative day 3 (17 IU/ml) but remained negative since then. His postoperative course was notable for hemorrhagic shock due to retroperitoneal hematoma, and delayed graft function. A biopsy a week after transplant continued to demonstrate diffuse mesangial proliferative GN along with acute tubular necrosis and thrombotic microangiopathy. The latter finding was attributed to calcineurin inhibitor–induced toxicity, and subsequently, tacrolimus was switched to belatacept. Thereafter, he has had an excellent allograft function with the last documented SCr level of 1.2 mg/dl. UACR had reached a nadir of 19 μg/mg; however, it increased to 1094 μg/mg approximately 2 years after the transplant so that a biopsy was performed which demonstrated negative immunofluorescence studies, consistent with the resolution of donor-derived HCV-related ICGN along with evidence of acute antibody-mediated rejection. Subsequently, he received intravenous immunoglobulin for the treatment of antibody-mediated rejection and UACR had improved to 540 μg/mg at the last follow-up visit (approximately 2 years and 4 months after transplant).

DISCUSSION

Although the Organ Procurement and Transplantation Network data between 2015 and 2022 show that the proportion of waitlisted patients willing to accept a deceased donor kidney from HCV-viremic donor increased 20-fold, a recent survey demonstrated that only 58% of transplant centers offer HCV-viremic kidneys to HCV-naïve recipients, and many kidneys from HCV-positive donors are still being discarded with the discard rate being stagnant at about 25%.[7-9]

Whereas trials of transplanting HCV-positive kidneys have been encouraging with good allograft outcomes in the relatively short term, clinical consequences of preexisting HCV-related injury in donor kidneys remain unknown given the absence of detailed donor biopsy results. In the first 2 trials to report outcomes for HCV-positive donor kidneys transplanted into HCV-negative recipients followed by direct-acting antiviral therapy, THINKER and EXPANDER trials, no data on procurement or postreperfusion biopsy results were reported.[1-3] In the MYTHIC trial, 5 HCV-naïve recipients developed proteinuria >1 g/d at a time interval >7 days posttransplant. Only 2 of them underwent kidney biopsies with the only described findings being acute tubular injury and pyelonephritis.[4] The THINKER-NEXT study, an ongoing multicenter trial, will provide additional insights into the presence and clinical consequences of renal allograft pathologic findings among HCV-viremic donors.

Our report suggests that preexisting HCV-associated kidney injuries are not rare and not readily apparent on procurement biopsies. This is likely due to the following: (i) the lack of postreperfusion biopsies with routine immunofluorescence panel, (ii) insensitivity of preimplantation biopsies, and (iii) their subtle pathologic features, because histologic pattern of donor-derived HCV-related IgM-dominant ICGN appeared less active than those seen in native kidney biopsies, likely reflecting the selection of donors without significant renal dysfunction.

In our current report, antiviral treatment reversed HCV-associated histologic changes in 2 patients by approximately 3 years and 2 years after transplant, respectively, whereas 1 patient had unchanged findings on subsequent for-cause biopsy for allograft dysfunction at 67 days posttransplant despite the absence of viremia. One patient did not undergo any posttransplant biopsy due to the lack of clinical indication. In the previously described case, a significant decrease in mesangial staining for IgM could be observed by day 100 posttransplant despite absence of viremia since posttransplant day 7.[6] Thus, it is conceivable that a repeat allograft biopsy at a later time point would have demonstrated a complete reversal of HCV-related pathologic changes in the latter 2 patients. With regard to the cause of glomerulopathy seen on reperfusion biopsies, a careful review of the clinical information available on DonorNet made chronic HCV infection the most likely cause rather than other potential causes for IC-mediated GN, including autoimmune diseases such as Sjogren's syndrome, chronic endovascular infection, and B or plasma cell malignancies.

Although its renal significance may be limited, proper diagnosis of donor-derived HCV-related IgM-dominant ICGN is important, because it can be misdiagnosed as duplication of the glomerular basement membranes of unknown significance, transplant glomerulopathy, or recurrent or *de novo* IC-mediated GN, especially when allograft biopsies are performed later in the course of transplant. Thus, immunofluorescence studies in selected cases and careful review of donor history are necessary.

Although we have opted not to include cases with only minimal mesangial staining for IgM (Fig. 1d) in this report to avoid overinterpretation of nonspecific trapping (usually trace intensity, without complements), it is not clear whether these may represent an attenuated form of the disease. Lastly, pathologists should be vigilant also for other forms of HCV-related kidney injury, such as fibrillary GN, mixed cryoglobulinemic GN, and AA amyloidosis from these donors.

To the best of our knowledge, there are no other reports of successful transplantation of HCV-positive kidneys with preexisting donor-derived HCV-associated injury. Although further long-term studies are needed, these cases support our prior conclusion that even kidneys from HCV-positive donors with histologic patterns of injury that are HCV-associated, when selected carefully, can be safely transplanted in HCV-negative patients with good short-term allograft outcome, likely due to the limited histologic activity, and thus limited clinical significance, and perhaps more importantly, the possible reversal of HCV-associated kidney injury after antiviral treatment.

DISCLOSURE

SM is a deputy editor of Kidney International Reports outside the submitted work; is supported by grants from National Institute of Health and Kidney Tx Collaborative; and has received consultation fees from HSAG and Sanofi, and royalties or licenses from Columbia University. LER participates on a data safety monitoring board/advisory board of Sanofi and Bristol Meyers Squibb and discloses stock ownership in Gilead Sciences and Hansa Biopharma. All the other authors declared no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Summary of clinical course by recipient. Graph depicting serum creatinine trend. Green bar denotes the time HCV detectable by PCR in serum. Red arrows denote the timepoints of the different kidney biopsies. Blue arrows denote hemodialysis discontinuation.

STROBE Statement.

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