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Tubuloreticular inclusions in peritubular capillaries of renal allografts

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ABSTRACT

Background: Tubuloreticular inclusions (TRIs) are anastomosing networks of microtubules that are frequently found in autoimmune diseases and viral infections. In renal allografts, TRIs have been reported in glomerular endothelial cells in association with viral infections and donor specific antibodies (DSAs), but their presence in peritubular capillaries has not been explored.
Methods: We collected seven cases with TRIs out of 148 consecutive renal allograft biopsies taken from Dec. 2015 to Dec. 2016.
Results: TRIs were present in peritubular capillaries in seven cases and were concomitantly present in glomerular endothelial cells in two cases. The diagnoses included polyomavirus nephropathy (n = 2), acute T cell-mediated rejection (ACR) (n = 1), combined ACR and antibody-mediated rejection (AMR) (n = 1), suspicious for ACR (n = 1), chronic active AMR (n = 1), and moderate tubular atrophy and interstitial fibrosis (n = 1). Six patients had recent or current viral infections (BK polyomavirus, hepatitis B virus, herpes simplex virus, and cytomegalovirus in two, two, one, and one case, respectively). DSA was positive in one case. Five cases had moderate to severe interstitial inflammation and four cases had peritubular capillaritis.
Conclusion: TRIs are not rare in peritubular capillaries. They are associated with various viral infections and their appearance seems to be related to peritubular capillary injury.

1. Introduction

Tubuloreticular inclusions (TRIs) are an anastomosing network of 18–26-nm microtubules and are principally found in endothelial cells. TRIs have been well-recognized in lupus nephritis and human immunodeficiency virus (HIV)-associated nephropathy of native kidneys [1–3], but they may appear in renal allografts. In a recent study of renal grafts, TRIs appeared in graft glomerular endothelial cells with a prevalence rate of 13.0% [4]. The authors claimed that TRIs were associated with viral infection and donor-specific antibodies (DSAs). However, further studies to support these findings have not been reported.

Like glomerular endothelial cells, peritubular capillaries are vulnerable as a target of alloimmune injury. Peritubular capillaritis and peritubular capillary C4d staining are considered to be morphologic features of acute/active antibody-mediated rejection (AMR). Furthermore, TRIs have been reported in peritubular capillaries in native kidneys with lupus [5], cytomegalovirus [6], and HIV infections [7]. We have looked for TRIs in renal allografts since late 2015. Herein, we report our experience with TRIs in seven renal allograft patients.

2. Material and methods

We retrieved 148 consecutive renal allograft biopsies from the archives of the Pathology Department between Dec. 2015 to Dec. 2016. These biopsies were studied with light, immunofluorescent, and electron microscopy. Ten cases did not contain glomeruli on the ultrastructural examination and three cases had only obso-

Abbreviations: ACR, acute T cell-mediated rejection; AMR, antibody-mediated rejection; DSA, donor-specific antibody; HIV, human immunodeficiency virus; TRI, tubuloreticular inclusion.

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Table 1
Clinical findings.

Case No.	sex	age	original disease	Type of donor	HLA mis-match	Immuno-suppression	Viral infection	Bx indication	Time to Bx, mo	S. Cr. at Bx (mg/dL)	S. Cr. at follow-up (mg/dL, mo)	Treatment	Remarks and clinical course
1	F	40	Unknown	LRD	1-haplo	FK + steroid	HBV, on tenofovir	Cr elevation, P	130	1.42	1.85 (10.5 mo)	Add mizoribine	
2	M	37	Unknown	LRD	1-haplo	CSA + steroid + MMF	HSV 8 mo previously, on famciclovir	Cr elevation	120	2.29	6.4 (12 mo)	Plasmapheresis and IVIG#6	Impending graft failure
3	F	60	Unknown	Deceased	1	FK + steroid + MMF	HBV-related liver cirrhosis, on entecavir, CMV 8 yrs previously	Cr elevation	102	2.15	1.6 (5 mo)	Steroid pulse	
4	F	35	IgAN	LRD	1-haplo	FK + steroid + MMF	no infection	Cr elevation	46	2.22	1.69 (8 mo)	Steroid pulse, ATG#4, and plasmapheresis #6	
5	M	62	Diabetic nephropathy	LURD	1	FK + steroid+ MMF	CMV (45,100 serum copies 5 mo previously, decreased to 1075 copies at the time of Bx), on cymevene	Cr elevation	5	3.6	6.3 (9 mo)	Steroid pulse	
6	M	51	IgAN	LURD	0	FK + steroid + MMF	BKV, on ciprofloxacin	Cr elevation	4	2.21	1.29 (1 mo)		ABO incompatible graft
7	F	60	Diabetic nephropathy	LURD	1	FK + steroid + MMF	BKV, on ciprofloxacin, cymevene	Cr elevation	6			Change from MMF to rapammune	CDC(−) FCM(+) DSA(+) graft

Bx, biopsy; LRD, living related donor; LURD, living unrelated donor; CSA, cyclosporine; FK, tacrolimus; MMF, mycophenolate; Cr, creatinine; P, proteinuria; BKV, BK polyomavirus; HSV, herpes simplex virus; HBV, hepatitis B virus; CMV cytomegalovirus; ACR, acute T cell mediated rejection; AMR, antibody mediated rejection; DSA, donor specific antibody; Tx, transplantation

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