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LETTER TO THE EDITORS

Glomerular galactose-deficient IgA1 detected in donor-derived and recurrent IgA nephropathy

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Dear Editors,

Galactose deficient IgA1 (Gd-IgA1) plays an important role in the pathogenesis of IgA nephropathy (IgAN) [1]. Immunofluorescence (IF) staining of KM55, a Gd-IgA1 specific monoclonal antibody, becomes an easy and reliable tool to detect Gd-IgA1 deposited in glomerular mesangium of IgAN [2–5]. To further understand the pathogenesis of IgAN, we investigated whether glomerular Gd-IgA1 deposition is sufficient to cause kidney damage or elicit clinically apparent disease, by examining KM55 staining in kidney allograft biopsies with donor-derived or recurrent IgAN.

We studied a cohort of 49 kidney allograft biopsies from 19 recipients with IgAN (six donor-derived, and 13 recurrent including 10 symptomatic and three asymptomatic; Table 1). All recipients with donor-derived IgAN showed equivalent mesangial staining for KM55 and IgA on their first post-transplant allograft biopsies (Figure S1). The intervals between transplant and biopsies range from 0 to 56 days (mean 4 weeks) after transplant. All of the three living unrelated donors are Caucasian with normal renal function without haematuria or significant proteinuria (one with trace proteinuria). These deposits were markedly reduced or disappeared on follow-up biopsies, consistent with the natural course of donor-derived IgAN reported previously [6–8].

All recurrent IgAN showed positive KM55 staining with similar intensity and distribution to IgA (Figure S1). The mean post-transplant time is 10 years in the symptomatic recurrent IgAN group compared with that of the asymptomatic recurrent IgAN group (<3 years). Notably, patient#1 in the asymptomatic recurrent IgAN group had five allograft biopsies, with negative IgA staining on the initial two biopsies (not shown) and positive IgA staining (1–2+ or 2+) on all the recent three biopsies. The interval between the first and most recent biopsy with IgA recurrence was 56 months. No significant histologic progression was identified with only very segmental mild mesangial hypercellularity in a few glomeruli (Oxford classification of M0E0S0T0C0 for all three biopsies). The patient has no significant proteinuria or haematuria over the total 6 years post-transplant follow-up. It is possible with longer observation, patients with asymptomatic recurrent IgAN may have clinical manifestation, as recurrence of IgAN is thought to be a time dependent phenomenon, with rates of recurrence increasing over post-transplant time [9].

The positive KM55 staining in donor-derived IgAN, especially from living asymptomatic donors, and asymptomatic recurrent IgAN with repeat biopsies and long clinical follow-up, raises the question that glomerular mesangial Gd-IgA1 deposition might not be sufficient to elicit kidney injury. We speculate glomerular deposition of Gd-IgA1, detected by KM55 staining, may reflect Gd-IgA1 polymers, such as Gd-IgA1 aggregates, Gd-IgA1/fibronectin and Gd-IgA1 immune complexes from circulation and/or in situ. Additional 'hits' such as complement activation or noncomplement mediators might be needed to elicit clinical IgAN.

Conflict of interest

All authors declare no conflicts of interest.

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Table 1. Demographics, baseline characteristics, biopsy findings and KM55 staining of the patients with donor-derived or recurrent IgAN.

	Age/ sex	Ethnicity	Original renal disease	Donor type	Prior transplant	Time post transplantation (months)	Serum Creatinine (mg/dl)	Haematuria (RBC/hpf)	Proteinuria (g/g Cr)	Oxford classification					Immunofluorescence staining intensity (0–4+)						Others
										M	E	S	T	C	G	A	M	C1q	C3	KM55	
Donor-derived IgAN																					
Pt1	38F	White	FSGS	LURDKT	1 (brother)*	0	NA	NA	NA	0	0	0	0	0	neg	2+	neg	neg	1+	1+	Total 6 bx, IgA and KM55 decreased and neg in 6 months
Pt2	63M	White	MPGN	DDKT	1 (wife)*	0.25	6.8	NA	NA	0	0	0	0	0	neg	2+	trace	neg	2+	2+	No rejection; no follow-up bx
Pt3	71M	White	DM-1	DDKT	0	2	2.6	NA	NA	0	0	0	0	0	1+	2+	1+	neg	trace	2+	No rejection; total 2 bx, marked decrease of IgA and KM55 in 2 months
Pt4	49M	White	HTN	LURDKT	0	1.5	2	1	0.35	0	0	0	0	0	neg	trace	neg	neg	neg	trace	ATI; total 4 bx, IgA and KM55 neg in 4 months, 9 months, and 3 years
Pt5	57F	White	Reflux Neph	LURDKT	0	0	NA	NA	NA	0	0	0	0	0	trace	1+	1+	neg	trace	1+	ATI; no follow-up bx
Pt6	49M	White	Reflux Neph	DDKT	1 DDKT*	2	1.7	0	–	0	0	0	0	0	neg	2+	trace	neg	trace	2+	No rejection; total 3 bx, IgA and KM55 neg in both 9 and 12 months
Symptomatic recurrent IgAN																					
Pt1	29F	White	IgAN	LRDKT (cousin)	1 (father)*	101	1.76	0–2†	1.5	0	0	0	0	0	2+	3+	2+	2+	trace	3+	Mixed rejection
Pt2	39M	White	IgAN	LDKT	0	185	2.07	0–2†	1.0	0	0	1	2	0	1+	2+	1+	neg	trace	2+	Mixed rejection
Pt3	55F	Asian	IgAN	DDKT	0	225	1.29	1†	1.82	1	0	1	0	0	1+	2+	1+	1+	1+	2+	TG
Pt4	39M	White	IgAN	LRDKT (mother)	0	212	3.07	1†	1.40	0	0	0	2	0	neg	3+	neg	neg	neg	3+	Severe global sclerosis
Pt5	27M	Asian	IgAN	LRDKT (sister)	0	24	1.05	4†	0.81	1	0	1	0	0	neg	3+	trace	neg	1+	3+	Mixed rejection
Pt6	60F	Asian	IgAN	DDKT	0	233	1.41	0–3†	2.30	1	0	1	1	0	trace	3+	2+	1+	2+	3+	No rejection
Pt7	38M	Asian	IgAN	DDKT	1 (LDKT)*	55	1.35	2–5†	2.00	1	1	0	0	0	1+	3+	neg	neg	1+	3+	TG
Pt8	26M	White	IgAN	LURDKT	0	40	1	79	1.20	1	0	1	0	0	trace	3+	neg	neg	1+	3+	No rejection
Pt9	76F	Asian	IgAN	DDKT	0	60	2.3	10–12	2.00	1	0	0	0	0	neg	3+	trace	neg	trace	3+	Mild diffuse diabetic nephropathy
Pt10	75M	Asian	IgAN	DDKT	0	156	2.2	1†	4.4	1	0	1	2	0	neg	2+	trace	neg	1+	trace	Thrombotic microangiopathy involving one glomerulus and arterioles

Table 1. Continued.

	Age/ sex	Ethnicity	Original renal disease	Donor type	Prior transplant	Time post transplantation (months)	Serum Creatinine (mg/dl)	Haematuria (RBC/hpf)	Proteinuria (g/g Cr)	Oxford classification					Immunofluorescence staining intensity (0–4+)						Others
										M	E	S	T	C	G	A	M	C1q	C3	KM55	
Asymptomatic recurrent IgAN																					
Pt1a	30M	Asian	IgAN	DDKT	1 (unknown)*	13	1.0	<1	0.07	0	0	0	0	0	neg	1–2+	neg	neg	neg	1+	Mild peritubular capillaritis
Pt1b						65	1.19	1	0.17	0	0	0	0	0	neg	2+	neg	neg	trace	2+	chronic and active AbMR; 2B cell mediated rejection
Pt1c						69	2.5	0–2	0.27	0	0	0	0	0	neg	2+	neg	neg	trace	2+	Chronic and active AbMR
Pt2	22F	Hispanic	IgAN	LURDKT	0	18	1	1	0.1	0	0	0	0	0	neg	1+	Trace	neg	neg	1+	Borderline cell mediated rejection
Pt3	23M	Burmese	IgAN	DDKT	0	63	1.32	1	0.2	0	0	0	0	0	neg	1+	neg	neg	neg	1+	FSGS

AbMR, antibody mediated rejection; ATI, acute tubular injury; bx, biopsy; DDKT, deceased donor kidney transplant; DM-1, type 1 diabetes; FSGS, Focal segmental glomerulosclerosis; HTN, hypertension; IgAN, IgA nephropathy; LURDKT, living unrelated donor kidney transplant; MPGN-1, type 1 membranoproliferative glomerulonephritis; neg, negative; Reflux neph, reflux nephropathy; TG, transplant glomerulopathy.

Donor-derived IgAN group (n = 6): (a) native kidney biopsy proven non-IgAN as the cause of ESRD, and (b) IgA deposition on initial post-transplant allograft biopsy/biopsies. Symptomatic recurrent IgAN group (n = 10): (a) native kidney biopsy proven IgAN as the cause of ESRD; (b) no IgA deposition on initial post-transplant allograft biopsy/biopsies; (c) IgAN diagnosed on follow-up allograft biopsy; and (d) proteinuria and/or haematuria at the time of biopsy. Asymptomatic recurrent IgAN group (n = 3): (a) native kidney biopsy proven IgAN as the cause of ESRD; (b) no IgA deposition on initial post-transplant allograft biopsy/biopsies; (c) IgAN diagnosed on follow-up allograft biopsy/biopsies; and (d) no proteinuria or haematuria at the time of biopsy. All recipients with ESRD secondary to IgAN have at least one prior biopsies with negative IgA staining (data not shown). All biopsies from donor-derived IgAN group were the first for cause biopsies and four recipients had follow-up biopsies summarized in column 'Others'.

*Allografts failed because of rejection. Allograft failed because of rejection, but there is also recurrent IgAN.

†The data reflected the test results at the time of the biopsies; all these recipients had gross or microscopic haematuria at times prior to the biopsies.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Representative kidney biopsy findings of donor-derived IgAN (a–d), asymptomatic recurrent IgAN (e–h) and symptomatic recurrent IgAN (i–l).

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