CEN Case Reports (2018) 7:268–273
https://doi.org/10.1007/s13730-018-0341-2

CASE REPORT

Recurrence of crescentic IgA nephropathy after renal transplantation

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Received: 20 March 2018 / Accepted: 19 May 2018 / Published online: 25 May 2018

Abstract
IgA nephropathy (IgAN) is one of the most common recurrent glomerulonephritis after renal transplantation. Rarely, it is accompanied with the presence of crescents that leads to rapid deterioration of renal function and graft loss. We present a 54-year-old patient with IgAN that received a cadaveric kidney allograft, but developed biopsy proven recurrent IgAN 7 months after renal transplantation. He was treated with intravenous steroids and angiotensin-converting enzyme inhibitor and remission was achieved. 4 years later, he presented again with heavy proteinuria, hematuria and deterioration of renal function. Allograft biopsy revealed recurrent IgAN with crescents, which was successfully treated with pulse intravenous steroids and six monthly doses of intravenous cyclophosphamide. This regime resulted in long-term sustained remission with a stable functioning graft 3 years later. Although it is not an established treatment as in native kidneys, intravenous cyclophosphamide should probably be considered in kidney transplants with potentially reversible recurrent crescentic IgAN.

Keywords IgA nephropathy · Renal transplantation · Recurrent glomerulonephritis · Crescents

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of glomerulonephritis worldwide, characterized by mesangial proliferation and diffuse deposition of IgA [1]. Up to 25% of the patients will progress to end stage renal disease (ESRD) within 10 years after diagnosis [2], but usually such patients have little comorbidities and represent ideal candidates for transplantation [3]. IgAN is also one of the most common recurrent glomerulonephritis after renal transplantation. It has been reported that 9–61% of the patients with primary IgAN that receive kidney allograft, will develop recurrent disease [4]. The wide range of the recurrence rate is partly explained by the different policies regarding protocol biopsies as well as the indications for allograft biopsy in each center [3, 4]. More often the recurrences occur after 3 years post transplantation [3, 5] and they affect graft survival only in the long term, associated with a twofold increase in the risk for graft loss [6]. Patients usually develop persistent hematuria and low-grade proteinuria, following a benign course, but rarely rapid deterioration of renal function may occur that is related with the presence of crescents [7]. We present a patient that developed recurrent IgAN during the first year after renal transplantation that progressed 4 years later to crescentic glomerulonephritis.

Case report

Our patient was diagnosed with IgAN in 2001, at the age of 40. He underwent renal biopsy due to declining renal function (serum Creatinine—sCr: 3 mg/dl) over a period of 3 months, which revealed glomeruli with mesangial proliferation and depositions of IgA. There was extensive interstitial fibrosis and 50% of the glomeruli were sclerosed, but he still received steroids for a period of 6 months

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with no improvement. He reached ESRD after 2 years and commenced hemodialysis in Dec 2003.

7 years later, in Sept 2010 he received a cadaveric kidney allograft. Basiliximab was administered as induction treatment, while maintenance immunosuppression treatment consisted of tacrolimus (Tac) 2 mg twice daily, mycophenolic acid (MPA) 500 mg twice daily and prednisolone (Pred). No allograft biopsy was obtained at the time of implantation. He was discharged with sCr: 1.2 mg/dl and no antihypertensive medication other than amlodipine 10 mg. During the next 7 months renal function was stable, blood pressure was under control, Tac levels (C0) were around 6 ug/l and he experienced no rejection episodes or CMV infections.

In Apr 2011, he was found to have hypertension (160/85 mmHg) with microscopic hematuria and proteinuria of 5 g/24 h, while his renal function remained stable. Allograft biopsy showed recurrence of IgAN with mesangial proliferation in > 50% of the glomeruli, but no crescents. Interstitial fibrosis and tubular vacuolization in < 10% of the specimen indicated a small degree of CNI toxicity. He received three daily doses of intravenous methylprednisolone (MP) 500 mg, continued with daily 40 mg po Pred for 2 months and tampered over another 4 months down to 5 mg per day. He also received maximum dose of quinapril 40 mg. He remained on Tac 2 mg twice daily (C0 target: 6 ug/l) and MPA 500 mg twice daily. For the next 4 years, renal function remained stable (sCr: 1.5 mg/dl) with a small degree of proteinuria (0.3–0.4 g/24 h) and microscopic hematuria.

In Jan 2015, proteinuria 3 g/24 h was noted in a regular follow-up appointment. During the next month renal function deteriorated (sCr: 2.1 mg/dl), while proteinuria increased to 9.8 g/24 h, combined with microscopic hematuria. Allograft biopsy showed again recurrence of IgAN with diffuse mesangial proliferation combined with cellular crescent formation and necrosis in 60% of the glomeruli (Figs. 1, 2, 3). Glomerulosclerosis and interstitial fibrosis accounted for < 20% of the biopsy specimen. ANCA were negative. He received MP pulse therapy (500 mg × 3) and six doses of intravenous cyclophosphamide 650 mg (500 mg/m^2) for the next 6 months, combined with small increase in Pred (30 mg) tampered over 3 months. During this 6 month period, MPA was halved to 250 mg twice daily, but not stopped, he remained on his usual dose of Tac (C0 target: 6 ug/l) and maximum dose of quinapril. No major side effect, such as pancytopenia or infection, was observed. Three years later, the patient is considered to be in remission with stable renal function (sCr: 1.6 mg/dl) and low-grade proteinuria (0.5–0.8 g/24 h), while receiving the initial regime Tac-MPA-Pred and maximum dose of quinapril 40 mg. The patient's clinical course is summarized in Fig. 4.

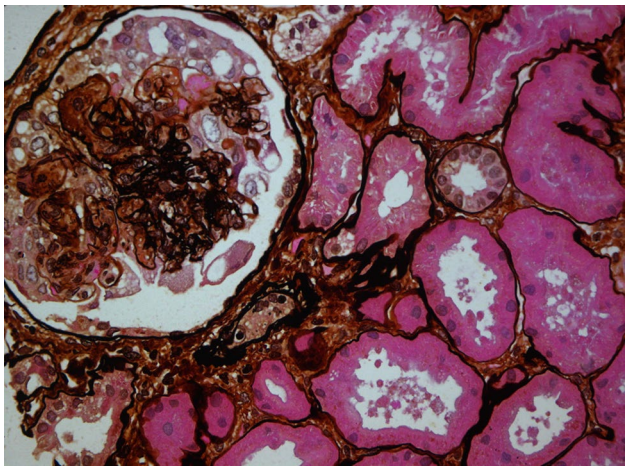

Fig. 1 Glomerulus with mesangial proliferation and crescent formation (Methenamine silver-periodic acid–Schiff stain ×400)

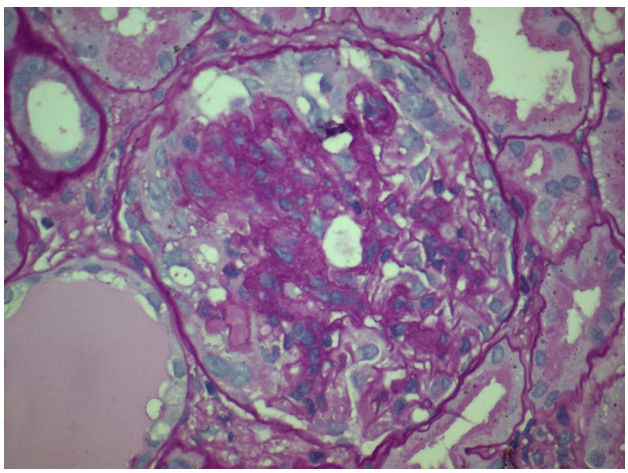

Fig. 2 Mesangial hypercellularity and full cellular crescent (Periodic acid–Schiff stain ×600)

Discussion

Crescentic IgAN is an uncommon finding in native kidneys, estimated to account for 3–5%, (when > 50% of glomeruli are involved by crescents) and 32% of IgAN cases (if any number of glomeruli are involved) [8]. The presence of crescents is even rarer in allograft kidneys, although it has been reported in 4–14% of recurrent or de novo allograft IgAN in Asian patients [9, 10]. Several case reports [11–20] and two case series have been published [7, 10] (Table 1). It appears to be a male predominance and the only factor associated with the development of crescentic IgAN is the presence of IgAN in native kidneys that led to ESRD [7, 10]. Mousson et al. speculated that

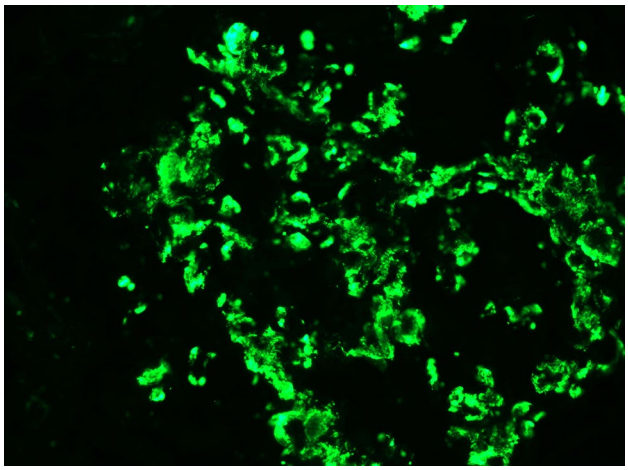

Fig. 3 Immunoflorescence staining for IgA showing dominant mesangial distribution (×600)

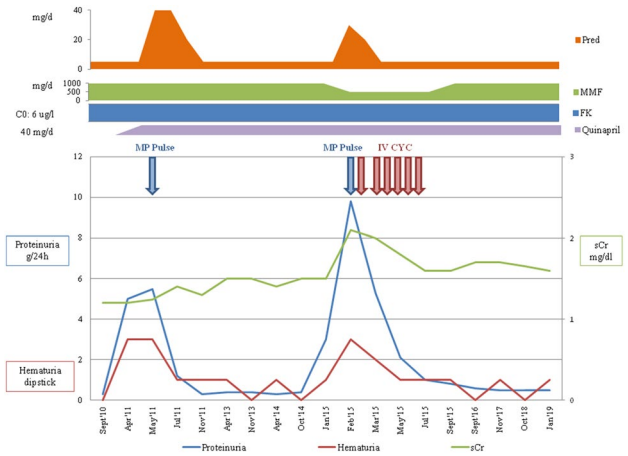

Fig. 4 Patient's clinical course. *Pred* prednisolone, *MMF* mycophenolate mofetil, *FK* tacrolimus, *MP* methylprednisolone, *CYC* cyclophosphamide, *sCr* serum creatinine

the presence of crescentic IgAN in native kidneys may be associated with the recurrence of crescents in the allograft, but this has not been reported elsewhere [17]. Tang et al. suggested that while in the majority of cases the immunosuppressive regimen consisted of Calcineurin inhibitor (CNI) + Azathioprine (Azp) + Pred, the establishment of mycophenolate mofetil (MMF) therapy may prevent the formation of crescents [10]. Disappointingly, patients on MMF still experience crescentic IgAN recurrence [17–19].

The presence of crescents in the allograft with IgAN is predictor of poor outcome [9]. Kowalewska et al. reported eight patients with allograft IgAN recurrence and crescent formation in only 7–30% of the glomeruli. Nevertheless, half of them returned to HD [7]. In the case series reported by Tang et al., the percentage of glomeruli with crescents was greater, from 10 to 66.7%, and nine out of ten patients experienced graft loss [10]. Various treatment strategies have been tried with poor outcomes, including pulse steroids, cyclophosphamide per os, plasma exchange and intensification of immunosuppressive regimen [7, 10]. Recently, Herzog et al. reported the use of eculizumab with no effect [19], while Katsumata et al. presented a patient with crescents in only 10% of the glomeruli, that achieved remission with tonsillectomy and steroid pulse therapy [20]. Our patient received pulse steroids and six monthly doses of intravenous cyclophosphamide. Remission was achieved and sustained, with a functioning graft 3 years later. We decided to administer such intensive immunosuppressive treatment because we considered the recurrence potentially reversible, as crescents were found in more than 50% of nonsclerosed glomeruli and the degree of glomerulosclerosis was relatively small < 20%. To minimize the overall immunosuppressive effect, we decided to administer only 0.5 mg/kg Pred (30 mg), quickly tampered over 3 months and lower the dose of MPA. Intravenous cyclophosphamide is recommended for crescentic IgAN in native kidneys by KDIGO guidelines with low quality of evidence [21], but it is not an established treatment in allograft recurrence. The same treatment has been reported to be successful only once, by Gopalakrishnan et al., in a patient with great extent of crescents (56%) as well, although the duration of sustained remission is not stated [18]. Herzog et al., before the unsuccessful use of eculizumab, tried intravenous cyclophosphamide with no effect, however, apart from IgAN recurrence, their patient suffered a long course of repeated graft-related infectious complications [19].

Conclusion

Treatment with intravenous cyclophosphamide is not recommended routinely in recurrent crescentic IgAN after renal transplantation as in native kidneys. There is always concern about the pros and cons of intensive immunosuppressants in transplant patients. Nevertheless, it should probably be considered, especially in patients with minimal glomerulosclerosis and potentially viable allograft.

Compliance with ethical standards

Conflict of interest The authors have declared that no Conflict of interest exists.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study. Additional informed consent was

Table 1 Clinical features of transplant recipients with crescentic IgAN, findings in kidney biopsy, treatment and outcome

References	Age (year)	Sex	Disease in native kidney	Time from Tx	Treatment protocol	Hematuria	Proteinuria (g/day)	Blood pressure (mmHg)	sCr (mg/dl)	Kidney Biopsy		Treatment	Outcome
										GS (%)	Crescents (%)		
[11]	54	M	IgAN	10 mo	CsA + MP	Gross	1.3	HT	9	NA	60	PEX, po CYC, po Pred	HD after 2 months
[12]	29	M	MPGN	5 mo	CsA + Pred	Microscopic	0.68	NA	3.8	NA	80	PEX, po CYC, MP pulse	HD after 4 months
[13]	52	M	IgAN	4 y	Azp + Pred	NA	NA	NA	7.1	NA	40	PEX, MP pulse	sCr: 1.8 mg/dl after 30 Days
[14]	51	M	NA	4 y	CsA + Pred	Microscopic	10.6	NA	11.6	NA	50	MP pulse	sCr: 2.5 after 12 months
[15]	46	M	NA	27 mo	CsA + MMF + Pred	Microscopic	10.13	NA	1.8	NA	66.7	CsA to Tac, warfarin	HD after 4 months
[16]	52	M	IgAN	10 mo	Tac + Azp + Pred	Microscopic	4.48	180/100	2.7	NA	33	Azp to MMF po Pred, ACEi	sCr: 3.7 md/dl after 6 months but deteriorating
[7]	43	M	IgAN	20 y	CYC + steroid	NA	3^+ dipstick	140/90	4.3	10	7	NA	HD after 12 months
[7]	48	M	IgAN	17 y	Azp + steroid	Microscopic	10.77	130/95	1.9	30–40	12.5	Azp, po steroid, ASA, propranolol	HD after 6 months
[7]	53	F	IgAN	6 y	Azp + CNI	NA	3.5	NA	2.3	14	20	NA	Unknown
[7]	41	M	IgAN	22 mo	CNI + steroid	NA	NA	140/84	5	28	30	MP pulse, PEX	HD after 1 month
[7]	59	M	PIGN	3 y	CNI + steroid	NA	NA	175/92	2.7	25	17	MP pulse	HD after 2 months
[7]	38	M	IgAN	9 y	CNI + Azp + steroid	NA	NA	140/88	2	15	7	ACEi	sCr: 1.6 mg/dl after 4 years
[7]	22	F	IgAN	3 y	CNI + Azp + steroid	Microscopic	3^+ dipstick	136/90	6.5	13	13	MP pulse, CNI, ACEi	sCr: 1.3 mg/dl after 5 years
[7]	37	M	reflux	5 y	CNI + MMF	Microscopic	1^+ dipstick	NA	2.7	4.8	14.3	Po steroid	sCr: 1.7 mg/dl after 6 years
[17]	NA	NA	IgAN	15 mo	NA	Microscopic	0.8	NA	2.8	NA	30	MP pulse	HD after 2 months
[17]	NA	NA	IgAN	47 mo	NA	Microscopic	2.4	NA	3.5	NA	20	MP pulse	HD after 27 months

Table 1 (continued)

References	Age (year)	Sex	Disease in native kidney	Time from Tx	Treatment protocol	Hematuria	Proteinuria (g/day)	Blood pressure (mmHg)	sCr (mg/dl)	Kidney Biopsy		Treatment	Outcome
										GS (%)	Crescents (%)		
[10]	26	M	IgAN	4 y	CsA + Azp + Pred	Gross	3.2	HT	3.56	30	60	MP pulse Azp to MMF	Re-transplant after 6 months
[10]	25	M	IgAN	5 y	CsA + Azp + Pred	Microscopic	1.8	HT	1.79	15	20	MP pulse Azp to MMF	HD after 6 months
[10]	28	M	NA	4 y	CsA + Azp + Pred	Microscopic	3^+ dipstick	HT	4.68	25	50	MP pulse CsA to Tac	HD after 1 year
[10]	28	M	IgAN	6.5 y	CsA + Azp + Pred	Microscopic	3.14	HT	3.73	20	66.7	MP pulse Azp to MMF	HD after 2 years
[10]	31	M	NA	6.5 y	CsA + Azp + Pred	Microscopic	1.5	HT	6.25	50	20	MP pulse CRRT	HD after 2 months
[10]	32	M	MPGN	6 y	CsA + Azp + Pred	Microscopic	1.88	Normal	2.83	15	20	MP pulse Azp to MMF	HD after 6 months
[10]	28	M	IgAN	3 y	CsA + MMF + Pred	Microscopic	2.05	HT	2.94	25	35.5	MP pulse CsA to Tac	HD after 3 years
[10]	48	M	IgAN	4 y	CsA + Azp + Pred	Microscopic	2^+ dipstick	HT	2.65	10	40	MP pulse Azp to MMF	Re-transplant after 5 years
[10]	69	F	Vasculitis	7 y	CsA + Azp + Pred	Microscopic	1.54	Normal	1.45	20	10	MP pulse CsA to Tac	sCr: 2.5 mg/dl stable after 3 years
[10]	45	F	APKD	4.5 y	CsA + MMF + Pred	Microscopic	1.36	HT	3.8	40	50	MP pulse CsA to Tac	HD after 8 months
[18][a]	20	M	Unknown	1 y	CsA + MMF + Pred	Gross	NA	NA	NA	NA	50	-	HD after 6 months
[18][a]	25	M	Unknown	3 y	Tac + MMF + Pred	Gross	uPCR: 5.1	NA	5.2	NA	56	MP pulse IV CYC	sCr: 1.8 mg/dl after 6 months
[19]	29	M	IgAN	2 mo	Tac + MMF + Pred	NA	13	NA	3.8	NA	60	IV CYC, po Pred Eculizumab	HD after 5 months
[20]	48	M	Unknown	10 y	Tac + MMF + MP	Microscopic	1.0	NA	1.8	30	10	Tonsillectomy, MP pulse	sCr: 1.7 mg/dl after 3 years

IgAN IgA nephropathy, *Tx* transplantation, *sCr* serum creatinine, *GS* glomerulosclerosis, *CsA* cyclosporine A, *MP* methylprednisolone, *HT* hypertension, *PEX* plasma exchange, *CYC* cyclophosphamide, *Pred* prednisolone, *HD* hemodialysis, *MPGN* membranoproliferative glomerulonephritis, *Azp* azathioprine, *MMF* mycophenolate mofetil, *Tac* tacrolimus, *ACEi* angiotensin converting enzyme inhibitor, *CNI* calcineurin inhibitor, *APKD* autosomal polycystic kidney disease, *Ref* reference, *M* male, *F* female, *NA* not available

[a]Same patient who received second kidney allograft

obtained from all individual participants for whom identifying information is included in this article.

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