Clinical Kidney Journal, 2022, vol. 15, no. 5, 1021–1023

https://doi.org/10.1093/ckj/sfac016
Advance Access Publication Date: 17 January 2022
Letter to the Editor

LETTER TO THE EDITOR

Early and late ANCA vasculitis relapses after kidney transplantation may have different presentations

Christophe Masset [1,2], Christine Kandel-Aznar[3], Jacques Dantal[1,2], Magali Giral[1,2], Maryvonne Hourmant[1,2], Gilles Blancho[1,2] and Claire Garandeau[1]

[1]Institut de Transplantation Urologie Néphrologie, CHU Nantes, Nantes, France, [2]Centre de Recherche en Transplantation et Immunologie UMR 1064, INSERM, Université de Nantes, France and [3]Service d'Anatomie et cytologie pathologiques, CHU Nantes, Nantes, France

Correspondence to: Christophe Masset; E-mail: christophe.masset@chu-nantes.fr

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) recurrence in kidney allografts is estimated at 0.1/patient/year, decreasing recently probably due to evolution in immunosuppression regimens [1]. Renal and extra renal recurrences are described, occurring in a median time of 30 months [2]. In our institution, 59 kidney transplants were performed for AAV recipients and among them 7 experienced recurrences, representing 12% of patients (Table 1). Four early recurrences (three patients) occurred immediately, presenting as primary non-function associated with extra renal symptoms. ANCA was highly positive in all cases at the time of transplantation. Transplant biopsies revealed crescentic and proliferative lesions requiring supplementary immunosuppressive treatment. Of four cases, three progressed towards end-stage renal disease (ESRD) at 3 months post-transplantation and all patients contracted fungal infections.

Three patients suffered late recurrences and these occurred several years after transplantation. The first case was a 58-year-old man presenting with urinary abnormalities 12 months after transplantation (haematuria and proteinuria). Allograft biopsy did not reveal any sign of AAV relapse at this time. Later, as the allograft function decreased, several other biopsies were performed and only the last one (fourth) satisfied a diagnosis of AAV recurrence (Figure 1). The second patient was a 73-year-old woman presenting with proteinuria and progressively impaired graft function about 3 years post-transplantation. Despite three normal allograft biopsies, a relapse diagnosis was only confirmed following bronchoalveolar lavage 3 years later. The third patient was a 67-year-old woman presenting asthenia and unexplained weight loss 4 years after transplantation. Explorations did not permit a diagnosis and kidney function decreased several months later, permitting a histological diagnosis of AAV recurrence. In all three late-relapse cases, initial clinical symptoms seemed attenuated and the ANCA titre was only slightly elevated and had risen late. Despite adaptative immunosuppressive treatment, two patients progressed towards ESRD.

Reports are scarce regarding AAV recurrence in relation to varying times post-transplantation. Our findings highlight that AAV recurrence can have different clinical presentations. Early recurrence has a noisy presentation, which is probably due to an underlying disease remaining active while on dialysis but with poor clinical symptoms. On the other hand, late recurrences had a more insidious presentation and were difficult to diagnose despite repeated allograft biopsies. This almost chronic clinical presentation leads to late diagnosis of flare-ups and thus late treatment, resulting in poor improvement of allograft function.

The most recent data suggest a prolonged maintenance treatment of at least 4 years to avoid AAV recurrence in native kidneys [3]. In transplantation, maintenance therapy with rituximab is not usually prescribed because of the concurrent anti-rejection immunosuppressive therapies. Nevertheless,

Received: 30.12.2021; Editorial decision: 11.1.2022

Table 1. Description of early and late AAV relapses

Patient	Sex	Age at relapse (years)	Last AAV flare	ANCA	AAV localization	AAV treatment	Transplantation	ANCA at transplantation[a]	Immuno-suppressive regimen	Suspicion of AAV relapse	Diagnosis of AAV relapse	ANCA at relapse, *n*	Localization of relapse	Treatment of relapse	Evolution
1	M	62	January 2013	MPO	R	CYP + steroids	June 2015	85	ATG + Tac/MMF/Cs	Month 6	Month 67	115	R + ER	RTX + steroids	ESRD
2	F	73	October 2009	PR3	R + ER	CYP + steroids	March 2014	32	ATG + Tac/CC/Cs	Month 33	Month 65	37	R + ER	RTX + steroids	ESRD
3	F	67	June 2011	PR3	R	CYP + steroids + PEX	November 2013	0	BSX + Tac/MMF	Month 58	Month 67	117	R + ER	RTX + steroids	CKD 4
4	F	61	April 2003	MPO	R + ER	CYP + steroids	September 2008 (1st)	947	BSX + Tac/MMF	Day 12	Day 12	604	R	CYP + steroids + PEX	ESRD
4	F	64	September 2008	MPO	R + ER	CYP + steroids	May 2011 (2nd)	252	ATG + Tac/CC/Cs	Day 6	Day 6	182	R + ER	Steroids + PEX	ESRD
5	M	67	September 2008	MPO	R	CYP + steroids	April 2016	67	BSX + Tac/MMF+Cs	Day 11	Day 11	26	R	Steroids	CKD 4
6	M	47	April 2001	MPO	R + ER	CYP + steroids	October 2005	160	BSX + Tac/MMF+Cs	Day 11	Day 11	150	R + ER	CYP + Steroids + PEX	ESRD

M: male; F: female; R: renal; ER: extra renal; CYP: cyclophosphamide; ATG: antithymocyte globulin; Tac: tacrolimus; MMF: mycophenolic acid; CC: mycophenolate mofetil; Cs: prednisone; RTX: rituximab; PEX: plasma exchange; CKD: chronic kidney disease.

[a]Before 2010, assessment of ANCA was performed using a Luminex method (BMD, Marne La Vallee, France), with a positivity threshold of 25, expressed in UA/L. From 2010, assessment of ANCA was performed using an enzyme-linked immunosorbent assay method (ImmunoCAP250, Thermo Fisher Scientific, Waltham, MA, USA), with a positivity threshold of 5, expressed in UI/L.

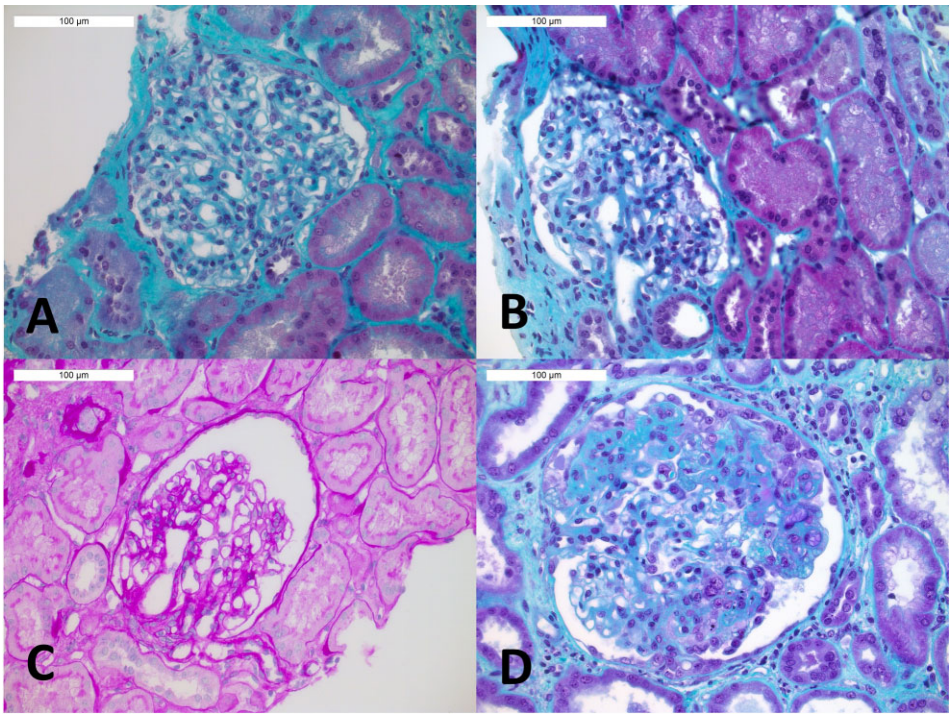

FIGURE 1: Histologic patterns were found in patient 1, for whom AAV relapse was diagnosed >5 years after initial suspicion. (**A**) First allograft biopsy performed at 12 months post-transplantation due to the appearance of haematuria without proteinuria or allograft dysfunction revealed no proliferation and no mesangial abnormality. Immunoglobulin A staining was negative (Masson's trichrome stain, ×400). (**B**) Second allograft biopsy performed at 3 years post-transplantation due to significant proteinuria (1.8 g/g) associated with persistent haematuria without allograft dysfunction revealed the absence of proliferative lesions and thus no argument for AAV relapse (Masson's trichrome stain, ×400). (**C**) Third allograft biopsy performed at 5 years post-transplantation due to acute kidney injury, persistent proteinuria and haematuria associated with non-atherosclerotic myocardial infarct and arthralgias', revealed stage 2 tubular atrophy/interstitial fibrosis with one glomerulus presenting focal segmental glomerulosclerosis lesion. No proliferation was seen (periodic acid-Schiff stain, ×400). (**D**) Fourth allograft biopsy performed 1 month later due to severe allograft dysfunction revealed endocapillary proliferation with segmental crescentic lesion, caryorexic elements and fibrin deposit leading to the diagnosis of AAV relapse.

it is possible that relief of immunosuppression maintenance therapy (notably antiproliferative drugs) several years after transplantation favours AAV recurrence. However, as immunosuppressive drugs are still ongoing, the clinical and even histological presentation can be torpid, thus delaying diagnosis and worsening the prognosis.

Our report highlights that late AAV recurrence in allograft transplants can be difficult to diagnose. In cases where AAV relapse is suspected, examinations should be repeated in order to begin adaptative treatment as soon as possible and to avoid evolution towards ESRD.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Gera M, Griffin MD, Specks U *et al*. Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosupression. *Kidney Int* 2007; 71: 1296–1301
2. Hruskova Z, Geetha D, Tesar V. Renal transplantation in anti-neutrophil cytoplasmic antibody-associated vasculitis. *Nephrol Dial Transplant* 2014; 30: i159–i163
3. Charles P, Perrodeau E, Samson M *et al*. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody–associated vasculitis. *Ann Intern Med* 2020; 173: 179–187