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Clinical Report

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Recurrence of ANCA-negative renal-limited pauci-immune glomerulonephritis in the renal allograft

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Abstract

Renal transplantation is the treatment of choice for end-stage renal disease (ESRD) due to pauci-immune crescentic glomerulonephritis (PICGN). A small subgroup of patients with PICGN are anti-neutrophil cytoplasmic antibody (ANCA) negative. We report a case of a patient with ANCA-negative renal-limited form of PICGN who developed ESRD despite treatment. He underwent live-related renal allograft transplantation after 12 months on haemodialysis. In the eighth post-transplant month, he developed graft dysfunction, which on evaluation turned out to be a graft recurrence of the basic disease in the form of PICGN. He received treatment with methylprednisolone, cyclophosphamide and plasmapheresis. However, his renal functions did not improve and he developed graft loss in the 11th post-transplant month and was started on continuous ambulatory peritoneal dialysis. We report a rare recurrence of renal-limited PICGN in the allograft. Patients with PICGN undergoing renal transplantation should be followed up carefully, and an early biopsy should be performed in the case of graft dysfunction to deal with this potentially graft-threatening complication.

Keywords: anti-neutrophil cytoplasmic antibody (ANCA); pauci-immune crescentic glomerulonephritis (PICGN); renal-limited vasculitis

Introduction

Crescentic glomerulonephritis (CGN) is the most aggressive structural phenotype in the continuum of injury that results from glomerular inflammation. The term rapidly progressive glomerulonephritis (RPGN) is also interchangeably used with the term CGN. Overall, PICGN is the commonest cause of CGN accounting for 60% of cases [1]. PICGN can lead to end-stage renal disease (ESRD) in 20% of cases despite treatment, and ANCA-associated vasculitis (AAV) accounts for 4% of case of ESRD in the UK [2]. Renal transplantation is generally considered the treatment of choice for ESRD secondary to PICGN. However, it can recur in the post-transplant period and can lead to graft loss. Hence, nephrologists should be aware of this potentially disastrous complication of PICGN in the post-transplant period.

Case report

A 16-year-old adolescent male had complaints of weakness, malaise, anorexia, nausea, fever and vomiting for a period of 4 weeks. The patient was investigated for the above problems at his primary health centre, and the investigation revealed severe anaemia and deranged renal functions. The patient was referred to our facility for the above problems. There was no history of skin rash, joint pains, oral ulcers or native/herbal medicinal intake. General physical examination revealed pallor, pitting pedal edema in both feet with a blood pressure of 160/90 mmHg. Systemic examination was unremarkable. The investigations revealed a hemoglobin level of 90 g/L (9 g/dL), total leukocyte count of 6600/cu mm and platelet count of 2×10^6 /cu mm. Urine examination showed a dipstick albumin of 3+ with a 24-h urine protein of 2.4 g and 15–20 red blood cells (RBCs)/high power field with RBC casts. Renal functions revealed a blood urea of 46.4 mmol/L (130 mg/dL) and a serum creatinine of 265.2 μmol/L (3 mg/dL), which had rapidly progressed to 884 μmol/L (10 mg/dL) after 7 days. Antinuclear antibody and ANCA were negative (by both enzyme-linked immunosorbent assay (ELISA) and immunofluorescence). The patient's serum tested negative for HBsAg, anti-hepatitis C antibody and human immunodeficiency virus. Serum complement levels were normal (C3/C4 = 120/40 IU/mL). Ultrasonography of the kidney, ureter and bladder revealed normal-sized kidneys (10 cm on either side) with a normal pelvicalyceal system. With a provisional diagnosis of rapidly progressive renal failure, a kidney biopsy was performed. Light microscopy revealed necrotizing glomerulonephritis with crescents (Figure 1). Direct immunofluorescence and electron microscopy did not reveal any immune complexes.

A diagnosis of ANCA-negative PICGN was made. A contrast-enhanced computerized tomogram of chest and

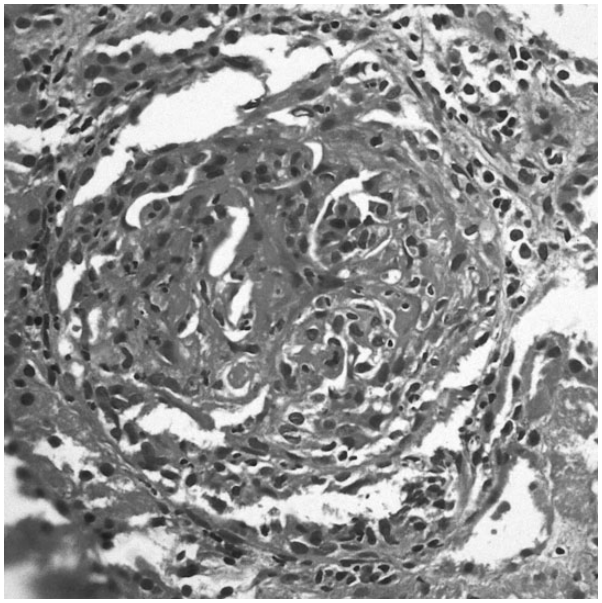

Fig. 1. A glomerulus showing cellular crescent. The underlying glomerular tuft shows a segmental necrotising lesion with disruption of the glomerular basement membrane, fibrin exudation and presence of karyorrhectic debris indicating small vessel vasculitis (H/E, ×400).

abdomen, which was done to look for evidence of extra renal vasculitic involvement, was normal. An ocular fundus examination carried by an ophthalmologist was unremarkable. With the diagnosis of ANCA-negative PICGN the patient was started on steroids (inj. methylprednisolone pulse 15 mg/kg for three consecutive days followed by 1 mg/kg/day of oral prednisolone) and monthly intravenous pulse cyclophosphamide therapy (12.5 mg/kg/pulse). His renal functions did not improve and he continued to be dialysis dependent for more than 3 months, so further cyclophosphamide pulse was not given and was declared ESRD. The patient underwent 12 months of hemodialysis before undergoing a live-related renal transplantation from his father. The patient received no induction and immunosuppression was comprised of tacrolimus (C0 was 11 ng/mL for first 3 months and then was maintained at 7 ng/mL), mycophenolate mofetil (2 g/day for first 3 months and then reduced to 1.5 g/day) and prednisolone (started at 0.5 mg/kg/day and was tapered and continued at 5 mg/day).

His immediate postoperative period was unremarkable but for a slow fall in serum creatinine, which remained at 176.8 µmol/L (2 mg/dL). A graft biopsy was done for the same, which revealed acute T-cell-mediated rejection. The patient was pulsed with methylprednisolone (500 mg for 3 days) and his serum creatinine came down to a baseline of 88.4 µmol/L (1 mg/dL). He was doing well with a creatinine level of around 88.4 µmol/L (1 mg/dL) till 8 months post transplant when he developed nausea, vomiting and loss of appetite. His investigations revealed a serum creatinine level of 176.8 µmol/L (2 mg/dL) and his urine analysis revealed albumin 2+ with 24-hour urine protein of 1.6 g and 15–20 RBCs with RBC casts. Serum creatinine progressed to 530.4 µmol/L (6 mg/dL) over 1 week. There was no evidence of obstruction or renal artery stenosis on duplex ultrasound examination. A kidney biopsy was performed. Light microscopy demonstrated necrotizing crescentic GN (Figure 2). Direct immunofluorescence and electron microscopy did not reveal any immune complexes, thus confirming a recurrence of PICGN.

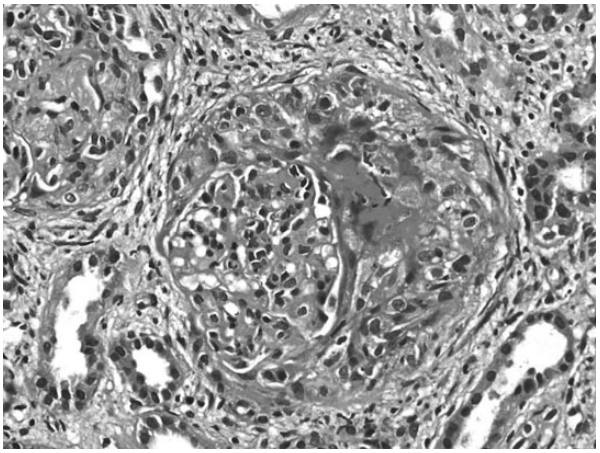

Fig. 2. One of the glomeruli shows cellular crescent with the presence of fibrin within the crescent. The underlying tuft shows segmental necrosis with fibrin exudation and presence of nuclear debris, thus confirming small vessel vasculitis (H/E, ×400).

His repeat ANCA was found to be negative by both ELISA and immunofluorescence. He was started on treatment along the lines of ANCA-related PICGN. His treatment with mycophenolate mofetil (MMF) was stopped and he was started on cyclophosphamide pulses (15 mg/kg every 2 weeks for three doses followed by three doses every 3 weeks) after giving pulse methylprednisolone (1 g/day for 3 days). His oral steroids were increased to 1 mg/kg/day for a period of 2 months and then tapered to 7.5 mg/day over next 4 months. Plasmapheresis was also initiated along with immunosuppression. Seven sessions (60 mL/kg/session) of plasmapheresis were given over a 2-week period. However, his renal functions worsened gradually and the serum creatinine had increased to 8 mg/dL over a period of 3 months. A repeat graft biopsy was performed which revealed predominantly chronic sclerosing glomerulonephritis. Graft loss was declared and he was started on continuous ambulatory peritoneal dialysis.

Discussion

Most cases of pauci-immune CGN (PICGN) can be attributed to systemic small vessel vasculitides, including granulomatosis polyangitis, microscopic polyangiitis and Churg–Strauss syndrome and renal-limited vasculitis [1]. These primary small vessel vasculitides are collectively known as AAV, in reference to their serological hallmark. However, a subgroup of patients with PICGN remain persistently negative for ANCA. In a large cohort of 213 patients with CGN, the likelihood of ANCA negativity was 20–30% when the intensity of staining for immunoglobulins was 0 and 1+, respectively (on a scale of 0–4+) [3,4].

ANCA-negative PICGN tends to present at a much younger age than its ANCA-positive counterpart [5–7]. Two studies compared the extra renal manifestations of patients with ANCA-negative PICGN with ANCA-positive counterparts in detail. In the study by Hedger *et al.*, ANCA-negative patients had fewer respiratory symptoms than ANCA-positive patients [7]. Chen *et al.* reported ANCA-negative PICGN had fewer constitutional and lesser extra-renal involvement than patients with ANCA positivity [5]. Renal involvement tends to be more severe in ANCA-

Table 1. Recurrence of PICGN in the renal allograft

Study	*n*	Follow-up (months)	Recurrence *n* (%)	Time at relapse (months)	Treatment	Outcome	ANCA status[a]
Lionel Rostaing *et al.* [12]	8	38 ± 17	1 (12.5)	10	MP, CYP	Improved	NR
G.Moroni *et al.* [13]	19	58 ± 57	7 (36.8)	45 (0.5–192)	MP, CYP	All improved[b]	NM
Nachman *et al.* [14]	127	–	12 (9.4)	31 (4–89)	MP, CYP, AZA	16.6% graft loss	NR
Nyberg *et al.* [15]	22	82 (4–132)	4 (18.18)	7–60	MP, CYP, PP	25% graft loss	NR
Geetha *et al.* [16]	85	64 (3–165)	3 (3.52)	>12	CYP, AZA to MMF	33.3% graft loss	NC
Little *et al.* [17]	107	66	5 (4.7)	–	–	60% graft loss	NR
Kai Ming *et al.* [18]	1	8	1 (100)	1	MP, CYP, PP	Graft loss	Neg

[a]At the time of transplantation, MP, methylprednisolone; CYP, cyclophosphamide; PP, plasmapheresis; NR, not related; NM, not mentioned; NC, not clear; Neg, negative; AZA, azathioprine; MMF, mycophenolate mofetil.
[b]At the last follow-up, the mean levels of serum creatinine and proteinuria were more elevated in patients with recurrence than in the other vasculitic patients.

negative PICGN than ANCA-positive PICGN across different ethnicities [5–8]. This may explain the poorer prognosis often documented in ANCA-negative PICGN [5,6]. Despite advances in the diagnosis and treatment, 20–40% of patients with PICGN develop ESRD and have to be treated with renal replacement therapy [9]. Our index patient also presented at a younger age, had no extra renal manifestations and had a severe renal disease progressing to end-stage renal failure despite the treatment offered. The pathogenesis of ANCA-negative vasculitis is not clear. An antibody against human lysosome membrane protein-2 (LAMP-2) was reported in the pathogenesis of vasculitis. However, a recent large study failed to show any mechanistic relationship between anti-LAMP-2 antibodies and glomerulonephritis [10].

Kidney transplantation is considered the treatment of choice in patients with ESRD due to pauci-immune glomerulonephritis. It was shown in a large retrospective analysis of 59 AAV patients with ESRD from a single center that transplanted patients had better survival than those who remained on dialysis [9].

Recurrence of vasculitis post transplant, particularly in the graft, can occur and can be graft threatening. In 1983, Curtis *et al.* described the first biopsy-proven recurrence of focal necrotizing glomerulonephritis in the graft [11]. Although no prospective data are available to assess the likelihood of recurrent PICGN after kidney transplantation, there are a few retrospective case series (Table 1) which have looked into the post-transplant renal recurrence and they have revealed a frequency of recurrent pauci-immune necrotizing GN varying from 4% to as high as 37% depending on different series.

However, recurrence of ANCA-negative PICGN is restricted to a single case report. Kai Ming *et al.* [18] had reported a 41-year-old Chinese woman who developed ANCA-negative PICGN along with systemic manifestations in the form of cutaneous, ocular and neural involvement. She received a cadaveric transplant a year later and in the first post-transplant month she developed renal, cutaneous and ocular relapse which showed partial response to plasmapheresis, cyclophosphamide and high-dose steroids. However, her renal functions steadily deteriorated and repeat biopsies showed persistent vasculitic changes. She lost her graft in the 8th post-transplant month. Her ANCA remained negative all throughout the course. Our index patient had recurrence of the disease at 8 months post transplant, but unlike the above-mentioned patient the recurrence was limited to the graft kidney without any extra-renal involvement.

Though there is not much evidence to delay transplantation in PICGN as far as the graft outcomes are concerned, it has been shown in multivariate analysis that kidney transplantation within 12 months of achieving remission was associated with increased mortality [17]. The optimal therapeutic management of recurrent PICGN is not clear, but the present day practice is similar to that of severe AAV and includes a combination of cyclosphosphamide, steroids and plasmapheresis [14,19]. Recurrent PICGN has been associated with poor long-term graft and patient survival [12,20].

In conclusion, we report a rare case of recurrence of ANCA-negative renal-limited vasculitis manifesting as PICGN in the grafted kidney. Delaying transplantation for a period of at least 1 year of extrarenal remission and early diagnosis of recurrence by a graft biopsy may help to deal with this potentially graft-threatening complication of PICGN.

Conflict of interest statement. None declared.

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