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ARTICLE

De novo pauci-immune glomerulonephritis in renal allografts

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Abstract

Pauci-immune glomerulonephritis in the native kidney presents with renal insufficiency, proteinuria, and hematuria, and is usually due to anti-neutrophil cytoplasmic antibodies. Rarely, kidney transplants can show this pattern as de novo disease. We performed a retrospective analysis in 10 cases of de novo pauci-immune glomerulonephritis. The mean time from transplant to diagnostic biopsy was 32 months (range, 4–96). All biopsies showed focal necrotizing or crescentic glomerulonephritis (mean 16% glomeruli, range 2–36%). Immunofluorescence and electron microscopy showed a pauci-immune pattern. No patients had evidence of systemic vasculitis. Anti-neutrophil cytoplasmic antibody results were available for 7 patients and were negative in all but one. Most patients had functioning grafts at one year after diagnosis. Two patients had repeat biopsies that showed continued active glomerulonephritis. We report the first clinicopathologic series of de novo pauci-immune glomerulonephritis which appears to be a unique pathologic entity that may occur early or late post-transplant and in our cohort is not associated with systemic vasculitis and usually not associated with anti-neutrophil cytoplasmic antibodies. The degree of crescent formation and renal impairment are milder than those of pauci-immune crescentic glomerulonephritis in the native kidney.

Introduction

Pauci-immune glomerulonephritis of the native kidney usually presents with acute or chronic renal insufficiency, hematuria, and proteinuria. Generally patients have systemic disease, usually affecting the lung or sinuses [1]. Most cases (about 90%) are associated with anti-neutrophil cytoplasmic antibody, or more specifically, anti-myeloperoxidase or anti-proteinase 3 antibodies [1, 2]. In vivo and in vitro studies have shown the potential of anti-proteinase 3 and anti-myeloperoxidase antibodies to directly contribute to kidney damage in the absence of immune complex formation [3–5].

In the native kidney, biopsy specimens under light microscopy characteristically show glomerular necrosis and crescents. Immunofluorescence microscopy shows no or minimal deposition of glomerular immunoglobulins or complement components. Electron microscopy shows concordantly no or minimal glomerular immune deposits [6]. Recurrence of pauci-immune glomerulonephritis in the renal allograft has been rarely described [7]; however, little is known about de novo pauci-immune glomerulonephritis of the transplanted kidney which is a rare but nonetheless existing entity [8].

The aim of the current study was to analyze the clinicopathological features of de novo pauci-immune glomerulonephritis of the renal allograft using a cohort of patients with renal biopsies reviewed in our institution.

Materials and methods

This study was approved by the Mayo Clinic Institutional Review Board. The authors declare adherence to the Declaration of Istanbul.

A retrospective analysis with clinicopathological correlation was performed in cases of de novo pauci-immune glomerulonephritis on kidney transplant biopsies diagnosed between January 2009 and January 2017. Protocol or clinically indicated biopsies were obtained from in-house patients ($n = 6$) and from patients from outside hospitals and reviewed at Mayo Clinic ($n = 4$).

For the purpose of this study, de novo pauci-immune glomerulonephritis was defined as new onset biopsy- proven

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pauci-immune glomerulonephritis at any time after transplant, in subjects with no history of pauci-immune glomerulonephritis in the native kidney and no pre-transplant history of anti-neutrophil cytoplasmic antibody positivity. Histologically, any evidence of glomerular crescents or necrosis by light microscopy, with no or minimal immune complex deposition by immunofluorescence or electron microscopy, would qualify for the diagnosis of pauci-immune glomerulonephritis, regardless of clinical presentation, hematuria, or proteinuria. By light microscopy, cellular crescents are defined as two or more layers of proliferating cells in Bowman's space with 50% of the lesion occupied by cells [9], while glomerular necrosis includes fibrinoid necrosis, karyorrhexis with nuclear debris and destruction of basement membrane. Light microscopy slides, immunofluorescence reports, and electron micrographs were reviewed at the initial biopsy with evidence of de novo pauci-immune glomerulonephritis and on available follow-up biopsies.

Clinical and laboratory data at the time of biopsy were reviewed, including serum creatinine, the degree of proteinuria, and the presence or absence of hemoglobinuria. For the in-house patients, measurement of anti-neutrophil cytoplasmic antibodies was performed using Inova fluorescein conjugated IgG goat anti-human immunoglobulin and in-house prepared ethanol fixed neutrophil slides; measurement of antinuclear antibodies and double strand deoxyribonucleic acid antibodies was also performed using indirect immunofluorescence assays (Inova and Bio-Rad Kallestad, respectively).

Standard processing of renal biopsies included light microscopy and immunofluorescence; glomeruli were available for electron microscopy on all but 2 initial biopsies. Deparaffinization of the light microscopy block was performed for electron microscopy on biopsies without material originally submitted for electron microscopy in glutaraldehyde fixative. For light microscopy, all cases were stained with hematoxylin and eosin, periodic acid–Schiff, Masson's trichrome and Jones methenamine silver as per routine for clinical renal biopsies. For immunofluorescence, 3 μm cryostat sections were stained with polyclonal fluorescein isothiocyanate-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen, albumin (Dako Corp.), and C4d (AbD Serotec), as per routine clinical testing. Immunofluorescence was scored by the pathologist on a 0 to 3 + scale.

Results

Clinical data at the time of diagnosis of de novo pauci-immune glomerulonephritis

Ten patients (5M, 5F) were identified that showed post-transplant de novo pauci-immune glomerulonephritis on biopsy, accounting for <0.001% of all kidney transplant biopsies during this time period (Table 1). Six patients were white, non-Hispanic/Latino, 2 African-American, 1 Hispanic/Latino and 1 Native American. The mean age was 51 years (range 26–78). The native kidney diseases were: lupus nephritis ($n = 3$), polycystic kidney disease ($n = 2$), diabetes mellitus ($n = 3$), interstitial nephritis ($n = 1$), and focal segmental glomerulosclerosis ($n = 1$). The mean serum creatinine at biopsy was 3.1 mg/dl (range 1.3–7.9). Five patients had hemoglobinuria and 4 had positive 24 h proteinuria (defined as urinary excretion >150 mg/day, mean 376 mg/24 h, range 192–861 mg/24 h) at the time of biopsy. No patient had >1 g/day proteinuria.

The mean time of biopsy was 32 months post-transplant (range 4–96 months); 3 biopsies occurred within the first 13 months post-transplant (see Table 1). Four biopsies showing de novo pauci-immune glomerulonephritis were protocol biopsies and 6 were for clinical indication with acute elevation of serum creatinine. In the setting of acute elevation of serum creatinine, de novo pauci-immune glomerulonephritis accounted for the cause of worsening renal function in 4 out of 6 cases (67%). In two cases, a status post-sepsis and BK virus associated nephropathy were considered the initial cause of increasing creatinine. Induction immunosuppression consisted of anti-thymocyte globulin, basiliximab or alemtuzumab. Four patients were on maintenance triple immunosuppression therapy with tacrolimus, mycophenolate mofetil, and prednisone; 1 patient was on therapy with tacrolimus, azathioprine, and prednisone; 3 patients were on tacrolimus and mycophenolate mofetil only; 1 patient was on tacrolimus and prednisone only, and 1 patient was on mycophenolate mofetil and sirolimus only. There was no evidence of systemic vasculitis in 9 patients; no information was available for 1 patient. Serum anti-neutrophil cytoplasmic antibodies, anti-myeloperoxidase, and/or anti- proteinase 3 results were available for 7 patients and were negative in all but one patient, who showed anti-neutrophil cytoplasmic antibodies positivity at a follow-up visit. One patient (#7) showed a high antinuclear antibody titer.

Biopsy findings at the time of diagnosis of de novo pauci-immune glomerulonephritis

All 10 biopsies showed a light microscopy pattern of focal necrotizing or crescentic glomerulonephritis (mean 16% glomeruli involved, range 2–36%) (see Table 2 and Figs. 1, 2 and 3). Specifically, one case showed 1 glomerulus with tuft necrosis without an associated crescent, five cases showed 1 glomerulus affected by cellular crescent, another biopsy showed 1 cellular crescent and 1 fibrocellular crescent, 8 cases showed segmental fibrous crescents of at least 1 glomerulus,. Overall, 8 cases showed fibrinoid necrosis. Eight out of 10 biopsies (80%) showed mild or no interstitial fibrosis, 1 biopsy showed moderate interstitial fibrosis

Table 1 Clinical Characteristics of our Patients

Patient #	Gender	Age	Native kidney disease	Biopsy time post-transplant (months)	Protocol or indication biopsy	Serum creatinine at biopsy (mg/dl)	24 h urine protein (mg)	Urinalysis proteinuria	Urinalysis hemoglobin	Antineutrophil cytoplasmic antibody, anti-myeloperoxidase and anti-proteinase 3	Induction therapy	Maintenance immunosuppression	Therapy after diagnosis of de novo pauci immune glomerulonephritis	serum creatinine at 2–3 months after biopsy (mg/dl)	serum creatinine at 1 year after biopsy (mg/dl)	serum creatinine at 1.5–2 years after biopsy (mg/dl)	Outcome
1	M	26	Interstitial nephritis (mesalamine related)	12	Protocol	1.9	168	not applicable/ available	positive, small	negative	Anti-thymocyte globulin	tacrolimus, prednisone, mycophenolate mofetil	Increased mycophenolate mofetil	1.7	1.5	1.5	functioning graft at last follow-up
2	M	73	Polycystic kidney disease	13	Indication, acute kidney injury following E. coli urosepsis	7.9	not applicable/ available	positive, 1 +	positive, 2+	negative	Anti-thymocyte globulin	tacrolimus, prednisone, mycophenolate mofetil	Started prednisone	4.2	3.1	3.5	death with graft function
3	F	54	Lupus nephritis	24	Protocol	1.5	72	negative	negative	negative	Basiliximab	tacrolimus, prednisone, azathioprine	Switched azathioprine to mycophenolate mofetil	1.8	1.1	1.6	death with graft function
4	F	56	focal segmental glomerulosclerosis, hypertension	4	Protocol	1.4	283	not applicable/ available	not applicable/ available	negative	Alemtuzumab	tacrolimus, mycophenolate mofetil	Started prednisone	1.6	1.3	1.5	functioning graft at last follow-up
5	F	35	Lupus nephritis, diabetes	53	Indication, acute kidney injury	2.6	861	not applicable/ available	not applicable/ available	negative	Alemtuzumab	tacrolimus, mycophenolate mofetil	Started prednisone	2.5	4.1	not applicable/ available	end-stage renal disease, underwent second kidney transplant
6	M	49	Diabetes	25	Protocol	1.3	192	negative	negative	negative	not applicable/ available	tacrolimus, mycophenolate mofetil	No change in therapy	1.0	1.1	not applicable/ available	functioning graft at last follow-up
7	F	78	Lupus nephritis	46	Indication, acute kidney injury	3.2	not applicable/ available	positive	positive	not applicable/ available	not applicable/ available	tacrolimus, prednisone, mycophenolate mofetil	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available	death with graft function
8	F	51	Polycystic kidney disease	96	Indication, acute kidney injury	4.8	not applicable/ available	positive	positive, large	negative	not applicable/ available	tacrolimus, prednisone, mycophenolate mofetil	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available	end-stage renal disease, dialysis
9	M	39	Diabetes, hypertension	56	Indication, acute kidney injury	3.3	not applicable/ available	positive, 1 +	positive, 2+	Positive cytoplasmic-anti neutrophils cytoplasmic antibody on follow-up	not applicable/ available	tacrolimus, prednisone	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available
10	M	49	Diabetes	14	Indication, acute kidney injury	8	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available	sirolimus, mycophenolate mofetil	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available	not applicable/ available

Table 2 Biopsy Findings at Diagnosis and Follow-up

INITIAL BIOPSY								FOLLOW UP BIOPSY	
Total number of glomeruli (light microscopy)	% Global glomerulosclerosis	Total number of glomeruli with cellular or fibrocellular crescents or fibrinoid necrosis (%)	Number of glomeruli with cellular or fibrocellular crescents (%)	Number of glomeruli with fibrinoid necrosis (%)	Segmental scars/ fibrous crescents present	% Interstitial fibrosis and tubular atrophy	Other biopsy findings	Follow-up biopsy timing (months)	Follow-up biopsy findings
47	2	1 (2%)	0 (0%)	1 (2%)	No	5	None	23	Focal pauci-immune crescentic glomerulonephritis with 1/12 (8%) glomerulus involved by a fibrocellular crescent
5	0	1 (20%)	1 (20%)	1 (20%)	No	5	Pyelonephritis	2	Acute tubular necrosis with moderate interstitial fibrosis and tubular atrophy, non-specific chronic inflammation.
8	38	2 (5%)	2 (5%)	0 (0%)	Yes	20	None	Not applicable	
9	11	5 (45%)	0 (0%)	5 (45%)	Yes	0	None	1	Focal pauci-immune necrotizing & crescentic glomerulonephritis (2/24 with cellular crescents/ necrosis, 8% of glomeruli)
7	43	1 (14%)	1 (14%)	1 (14%)	Yes	30	None	Not applicable	
18	0	1 (6%)	0 (0%)	1 (6%)	Yes	0	None	Not applicable	
22	18	1 (4%)	1 (4%)	0 (0%)	Yes	10	None	Not applicable	
4	0	1 (25%)	1 (25%)	1 (25%)	Yes	10	None	Not applicable	
8	38	3 (37.5%)	2 (25%)	1 (12.5%)	Yes	20	Acute tubular injury, very focal BK polyoma virus infection	Not applicable	
30	10	2 (7%)	1 (3.5%)	1 (3.5%)	Yes	80	Acute and chronic cellular rejection	Not applicable	

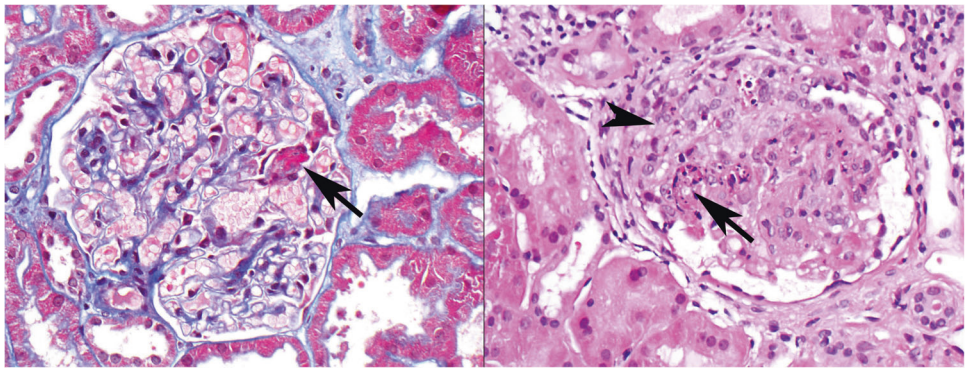

Fig. 1 By light microscopy, glomeruli show focal and segmental necrosis (arrow, left panel), cellular crescents (arrowhead, right panel), or karyorrhexis (arrow, right panel). The left panel is a Masson's trichrome stain from case #1 and the right panel is a hematoxylin & eosin stain from case #5

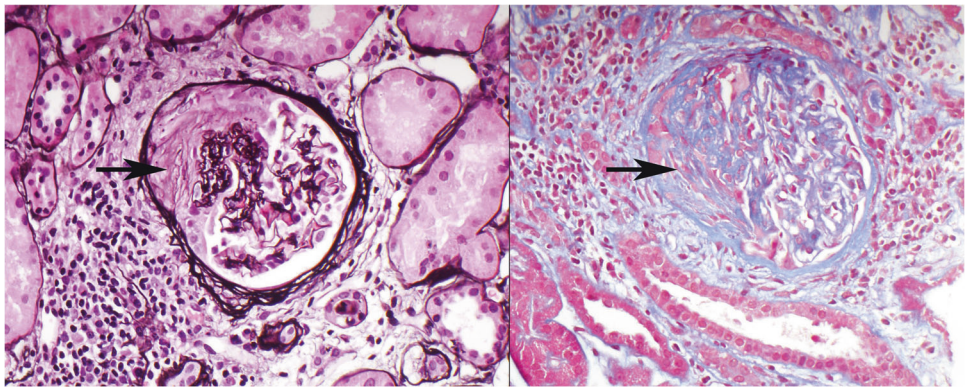

Fig. 2 : Two different glomeruli show fibrous crescent. The left panel is a Jones methenamine silver stain, the right panel is a Masson's trichrome stain; both from case #3

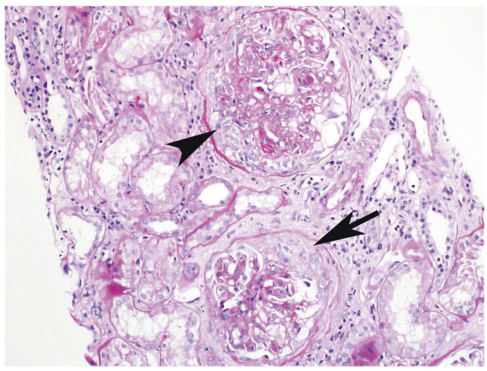

Fig. 3 These glomeruli show a range of cellular to fibrocellular to fibrous crescents. In this example, there is one glomerulus that shows a fibrocellular crescent (arrow) and another glomerulus that shows a cellular to fibrocellular crescent (arrowhead); periodic acid-Schiff from case #9

while 1 biopsy showed severe interstitial fibrosis. Eight out of 10 biopsies showed no significant interstitial inflammation or tubulitis (Banff i0 and t0 scores), while 2 showed moderate to severe interstitial and tubular inflammation consisting mostly of mononuclear cells and rare neutrophils. The diagnoses on the two cases with significant interstitial inflammation were acute and chronic cellular rejection (including transplant arteriopathy) and pyelonephritis. Another biopsy showed acute tubular injury and a single BK polyoma virus positive cell by in-situ hybridization but with minimal interstitial inflammation. Immunofluorescence and electron microscopy showed no evidence of immune complex glomerulonephritis in all biopsies. No necrotizing arteritis was present in any sample.

Clinical management after diagnosis of de novo pauci-immune glomerulonephritis

After the diagnosis of de novo pauci-immune glomerulonephritis, different therapeutic decisions have been made by the clinicians and the information was available in 6 patients (Table 1). In one of the patients treated with mycophenolate mofetil, tacrolimus and prednisone at baseline, the dosage of mycophenolate mofetil was increased. Despite this, the serum creatinine did not decrease (values between 1.5 and 1.7 mg/dL). One patient who had initially been managed with triple immunosuppression had been changed to a steroid-free regimen but, after the diagnosis of de novo pauci-immune glomerulonephritis, prednisone was restarted with reduction of creatinine (from 2.6 mg/dL to 1.6 mg/dL). One patient on prednisone and tacrolimus only had azathioprine added to the maintenance therapy. However, after one year, decreased renal function was observed (serum creatinine from 1.5 mg/dL to 1.8 mg/dL) and azathioprine was then replaced with mycophenolate mofetil. This change was followed by improved renal function (follow-up serum creatinine 1.1 mg/dL). One of the patients treated with mycophenolate mofetil and tacrolimus had prednisone added to

their therapeutic regimen with improved renal function (serum creatinine from 1.6 to 1.4 mg/dL). Another patient previously on mycophenolate mofetil and tacrolimus had prednisone added. This patient's renal function eventually declined and a second renal transplant needed to be performed. One patient treated with tacrolimus and mycophenolate mofetil had no change in treatment.

Follow-up laboratory and clinical data

After the diagnosis of de novo pauci-immune glomerulonephritis, mean serum creatinine within 3 months from biopsy was 2.1 mg/dL (range 1–4.2), at 1 year was 2 mg/dL (range 1.1–4.1) and at 2 years was 2.2 mg/dL (range 1.5–3.5; see Table 1). The latest mean serum creatinine available was 1.6 mg/dL (range 1.1–2.3) and was obtained at a mean of 35 months after biopsy (range 7–78).

Serum anti-neutrophil cytoplasmic antibodies, anti-myeloperoxidase, and/or anti- proteinase 3 results were available in 8 patients. Only one patient showed anti-neutrophil cytoplasmic antibodies positivity (specifically, cytoplasmic anti-neutrophil cytoplasmic antibodies) at a follow-up check after the biopsy.

Five grafts out of 10 were lost (Table 1). One patient developed chronic pyelonephritis (also present in prior allograft biopsies) with no pauci-immune glomerulonephritis identified on a follow-up biopsy, and died due to end-stage renal disease 1.5 years after the diagnosis of de novo pauci-immune glomerulonephritis. Another patient had no follow-up biopsies and died with a functioning graft 1.5 year after the diagnosis of de novo pauci-immune glomerulonephritis. The cause of death for this patient is unknown but the patient also had a diagnosis of stage IV non-small cell lung cancer. One patient died with a functioning graft 7 months after the diagnosis of de novo pauci-immune glomerulonephritis of unknown cause and no follow-up biopsies were available. One patient developed end-stage renal disease three years after the diagnosis of de novo pauci-immune glomerulonephritis, managed with dialysis (follow-up biopsy for this patient was not performed). One patient had a second kidney transplant for allograft failure 1 year after the diagnosis of de novo pauci-immune glomerulonephritis (but no allograft biopsy was performed at the time of worsening renal function).

Three allografts are still functioning. At 1.5 year after the initial diagnostic biopsy, one patient had persistent de novo pauci-immune glomerulonephritis with stable serum creatinine level. Another patient had persistent de novo pauci-immune glomerulonephritis at 1 month after initial diagnosis; however, a 3 years follow-up biopsy showed mild de novo IgM-dominant mesangioproliferative glomerulonephritis, with no evidence of crescents and necrosis. Serum creatinine was also stable. Lastly, one patient was clinically stable at 1 year after biopsy.

First follow-up biopsy findings

An initial follow-up biopsy was available in 3 patients (Table 2). The mean time length after diagnosis of de novo pauci-immune glomerulonephritis was 8.5 months (range 1 to 23). One patient showed focal crescentic glomerulonephritis with one glomerulus involved by a fibrocellular crescent without necrosis; mild arteriolar hyalinosis was also identified. This patient had a second more recent biopsy (87 months after diagnosis of de novo pauci-immune glomerulonephritis) which showed persistent focal sclerosing glomerulonephritis with no evidence of an active necrotizing or crescentic glomerulonephritis; severe arteriolar hyalinosis was also present. Another patient showed persistent necrotizing and crescentic glomerulonephritis with cellular crescents and necrosis involving 2 glomeruli; other glomeruli exhibited endocapillary hypercellularity and no additional findings. Another patient did not show ongoing active pauci-immune glomerulonephritis, but signs of chronicity were identified such as moderate tubular atrophy, interstitial fibrosis, and non-specific chronic inflammation.

Discussion

The current study analyzes 10 patients with well-characterized biopsy features and the clinicopathological aspects of an extremely rare (<0.001% of all kidney transplant biopsies) and ill-defined entity: de novo pauci-immune glomerulonephritis of the renal allograft. While the number of cases discussed is relatively small, this is the largest collection of such cases and provides necessary information in an area where there is minimal literature.

The first case report of a presumed de novo anti-neutrophil cytoplasmic antibodies-associated vasculitis of the transplanted kidney was published in 2000 by Asif et al. [10, 11]. This case described a 38-year-old woman with an unknown native kidney disease. Fourteen years after transplant, the patient developed a systemic vasculitis involving the kidneys and central nervous system, associated with a positive perinuclear anti-neutrophil cytoplasmic antibodies and anti-myeloperoxidase. The renal allograft biopsy showed necrotizing glomerulonephritis with crescent formation and no immune complex deposits. Later, a second case was reported by Tabata et al. [12]. This paper described a 34-year-old woman with a history of IgA nephropathy who developed new onset anti-myeloperoxidase-associated vasculitis involving the kidney only, nearly 15 years after kidney transplant. The renal biopsy showed crescentic glomerulonephritis with destruction of the Bowman's capsule and interstitial inflammation with peritubular capillaritis; no glomerular immune deposits were identified. A more recent case report by Haruyama et al. [13] also described a 61-year-old woman

who presented with presumed de novo renal-limited anti-neutrophil cytoplasmic antibodies-associated glomerulonephritis 31 years after kidney transplant. The native kidney disease was attributed to a chronic glomerulonephritis. The renal allograft biopsy showed crescentic glomerulonephritis with no immune complex deposits. All three of the cases described necrotizing or crescentic glomerulonephritis as a biopsy finding as well as positive serologic studies for anti-neutrophil cytoplasmic antibodies. Of note, all experienced pauci-immune glomerulonephritis very late post-transplant (14–31 years). Two patients did not have well-documented native kidney diseases, and so these were presumed to represent de novo glomerulonephritis.

In the current series, we found an equal number of male and female patients, with a variety of native kidney diseases. de novo pauci-immune glomerulonephritis can occur in the presence of elevated serum creatinine at the time of renal biopsy, or can be seen on a protocol renal biopsy with stable graft function, and patients may have hematuria or mild proteinuria regardless the reason of the biopsy (protocol versus indication). We did not appreciate definitive different clinical course between those diagnosed by protocol biopsy and those that had interstitial inflammation. The diagnosis of de novo pauci-immune glomerulonephritis may occur at any time after kidney transplant, ranging from within the first year up to 8 years post-transplant in this series. All patients were taking immunosuppressive therapy at the time of diagnosis of de novo pauci-immune glomerulonephritis. We had additional clinical information for 9 patients; none had evidence of systemic vasculitis (in particular, no lung or sinus involvement).

Notably, anti-myeloperoxidase and anti- proteinase 3 and/or anti-neutrophil cytoplasmic antibodies studies were negative in all but one of our patients with available data. To our knowledge, false negative anti-neutrophil cytoplasmic antibody results due to immunosuppression have not been previously described in the literature.

Also, this finding is in contrast to pauci-immune glomerulonephritis in the native kidney, in which ~85% of patients have positive anti-neutrophil cytoplasmic antibodies. The lack of association of pauci-immune glomerulonephritis with anti-neutrophil cytoplasmic antibodies in the transplant kidney raises the possibility of a different pathologic mechanism in these patients. Anti-neutrophil cytoplasmic antibodies negativity would argue against a role played by these antibodies in mediating the pathogenesis of the renal damage we observed. However, other anti-neutrophil cytoplasmic antibodies subtypes or cross-reacting antibodies could still be implicated in this phenomenon [14], directly or through complement activation, using inflammatory pathways not targeted by the immunosuppressant drugs administered. Of interest, while there were a variety of native kidney diseases in these 10 patients, 3 (30%) had a history of lupus, which raises the possibility of immune dysregulation that conceivably contributes to pathogenesis. Other differences between de novo pauci-immune glomerulonephritis in the transplant versus native kidney include the lack of systemic disease such as lung hemorrhage and a lack of systemic symptoms.

Importantly, according to the Revised 2012 Chapel Hill Classification [15], the renal-limited anti-neutrophil cytoplasmic antibodies-associated glomerulonephritis is a limited expression of a systemic vasculitis and should not be considered a single-organ vasculitis. However, in the current series, de novo pauci-immune glomerulonephritis is not associated with anti-neutrophil cytoplasmic antibodies and could potentially be re-classified under a different category of small vessel vasculitis.

In the current cases of de novo pauci-immune glomerulonephritis, the disease had different outcomes. In 2 patients, the disease persisted on follow-up biopsy, without worsening of renal function. In the case where continued glomerulonephritis was not identified on a follow-up biopsy, other disease processes likely to end-stage renal disease. The patient who received a second kidney transplant after the diagnosis of de novo pauci-immune glomerulonephritis had a 5 year follow-up biopsy of the new allograft which did not show any evidence of pauci-immune glomerulonephritis. Overall, compared to pauci-immune glomerulonephritis of the native kidney, de novo disease seems to be histologically less severe, and to correlate with a better prognosis than in the native kidney, which can be characterized by a rapidly progressive course [16]. Interestingly, when comparing de novo disease with recurrent pauci-immune glomerulonephritis of the renal allograft, data available show that the incidence of the latter is not reduced with immunosuppressant (i.e., cyclosporine A) and anti-neutrophil cytoplasmic antibodies negativity [17, 18]. To some extent, these findings may suggest possible clinical similarities between de novo and recurrent pauci immune glomerulonephritis.

The possibility of describing a very rare and severe phenotype of rejection, given that necrotizing arteritis is included in the Banff Classification [19] and it might be present in the glomeruli, has been taking into consideration. However, other features of cellular or antibody-mediated rejection are not consistently or significantly present, making this hypothesis less likely.

There are no guidelines for the management of this form of glomerulonephritis in the transplant setting. The usual treatment of anti-neutrophil cytoplasmic antibodies-positive and anti-neutrophil cytoplasmic antibodies-negative pauci-immune glomerulonephritis in the native kidney is characterized by induction therapy (usually with cyclophosphamide or rituximab, with or without steroids) followed by maintenance therapy (often less toxic immunosuppressive modalities such as mycophenolate mofetil or methotrexate). In our cases, the clinicians made their treatment decisions based on the clinical

signs and symptoms of the patient, and on the immunosuppressive therapy that was already prescribed. Stabilization and/or resolution of the disease not always happened, but multiple morbidities affecting the patient and different degree of severity of de novo pauci-immune glomerulonephritis could account for the different outcomes.

The current study has some limitations. For four patients we had limited access to their medical and laboratory records; this could potentially result in a non-complete picture of their clinical condition. We were able to assess the renal function using creatinine levels; glomerular filtration rate and/or slopes of inverse creatinine would have been a more accurate way to estimate it. We have the cause of native end-stage kidney disease documented by biopsy only for one patient; hence, a recurrence of undiagnosed pauci-immune glomerulonephritis, although unlikely, cannot be totally excluded. The anti-neutrophil cytoplasmic antibodies status of our cohort is not available in the pre-transplant setting; however, the absence of a clinical diagnosis of a systemic vasculitis at that time makes anti-neutrophil cytoplasmic antibodies positivity unlikely in these patients. Finally, this is a retrospective series and we can mainly speculate about the pathogenesis and implications of this disease pattern.

In conclusion, based on our findings, post-transplant de novo pauci-immune glomerulonephritis is a clinically variable lesion that does not seem to be exclusive of any sex, age or race; it may occur in patients with a variety of native kidney diseases; it may develop at any time after transplant; and it occurs in the setting of a variety of induction and maintenance immunosuppression regimens. This disease seems to be renal-limited rather than systemic and tends not to be associated with anti-neutrophil cytoplasmic antibodies. Although extremely rare, this disease of the renal allograft should be recognized as a distinct entity.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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