Clinical and pathological features of kidney transplant patients with concurrent polyomavirus nephropathy and rejection-associated endarteritis

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Abstract

AIM: To describe the clinicopathologic features of concurrent polyomavirus nephropathy (PVN) and endarteritis due to rejection in renal allografts.

METHODS: We searched our electronic records database for cases with transplant kidney biopsies demonstrating features of both PVN and acute rejection (AR). PVN was defined by the presence of typical viral cytopathic effect on routine sections and positive polyomavirus SV40 large-T antigen immunohistochemistry. AR was identified by endarteritis (v1 by Banff criteria). All cases were subjected to chart review in order to determine clinical presentation, treatment course and outcomes. Outcomes were recorded with a length of follow-up of at least one year or time to nephrectomy.

RESULTS: Of 94 renal allograft recipients who developed PVN over an 11-year period at our institution, we identified 7 (7.4%) with viral cytopathic changes, SV40 large T antigen staining, and endarteritis in the same biopsy specimen, indicative of concurrent PVN and AR. Four arose after reduction of immunosuppression...
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For the purpose of our study PVN was defined by the presence of typical viral cytopathic effect on routine sections stained by hematoxylin and eosin (H and E) and periodic acid-Schiff (PAS) methods and positive Polyomavirus SV40 large-T antigen (TAg) expression in tubular epithelial nuclei by standard immunohistochemistry (Ab-2, Oncogene Research Products, Cambridge, Massachusetts)\(^{6-9,19}\). AR was identified by intimal arteritis (v1 or more by Banff criteria) with or without staining of the peritubular capillaries for C4d by indirect immunofluorescence (clone 10-11, Biogenesis, Burlingame, California)\(^{10,14,23}\). All renal allograft biopsies were routinely stained for C4d in the period of study. Staining methods for tubular SV40 TAg expression were performed as described previously\(^{4,15}\). Tubules were considered TAg positive if 1 or more nuclei in a given profile was positive. A numeric score for quantification of TAg expression in tubular profiles was devised as follows: 0 = no detectable TAg, 1 = 1%-10%, 2 = 11%-20%, and so forth to a maximum score of 10 when 91%-100% of tubules had TAg staining. The average across all fields at 200 × magnification was converted to a percentage to reflect the extent of tubular infection. Two separate pathologists reviewed all cases; inter-rater agreement for TAg scoring was assessed using the intraclass correlation coefficient (ICC)\(^{24}\). Cases were also scored according to the Drachenberg system\(^{25}\).

Chart review was performed in compliance with

(1) (for treatment of PVN in 3 and tuberculosis in 1), and 3 patients had no decrease of IS before developing simultaneous concurrent disease. Treatment consisted of reduced oral IS and leflunomide for PVN, and anti-rejection therapy. Three of 4 patients who developed endarteritis in the setting of reduced IS lost their grafts to rejection. All 3 patients with simultaneous PVN and endarteritis cleared viremia and were stable at 1 year of follow up. Patients with endarteritis and PVN arising in a background of reduced IS had more severe rejection and poorer outcome.

CONCLUSION: Concurrent PVN and endarteritis may be more frequent than is currently appreciated and may occur with or without prior reduction of IS.

Key words: Acute rejection; BK polyomavirus; Kidney transplant; Polyomavirus nephropathy

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Core tip: Here we report the clinical and pathologic features of 7 cases of concurrent polyomavirus nephropathy (PVN) and endarteritis identified out of 94 renal allograft recipients who developed PVN over an 11-year period (7.4%). These cases arose both in the setting of a prior reduction in immunosuppression (IS) and without such a change. Therefore, concurrent PVN and endarteritis appears more frequent than currently reported in the literature and may occur with or without prior reduction of IS.

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INTRODUCTION

Many disease processes can limit the success of kidney transplantation, including cellular (T cell-mediated) rejection, antibody-mediated rejection (AMR), and polyoma virus nephropathy (PVN)\(^{1,2}\). The pathologic distinction between acute rejection (AR) and PVN may not be straightforward, as tubulointerstitial inflammation is a feature of both processes\(^{1-9}\). Intimal arteritis or endarteritis is a pathognomonic lesion of AR and is diagnostic of this disorder\(^{10,11}\). Classically considered a manifestation of T cell-mediated rejection, recent reports suggest that endarteritis can also be seen in association with donor specific antibodies, and may be indicative of mixed T cell-mediated and AMR\(^{1,2,9,10-13}\). Peritubular capillary C4d staining is a feature strongly suggestive of AMR, and like endarteritis, is not a feature of PVN\(^{1,9,14-18}\). Interstitial hemorrhage, plasma cells and neutrophils are more common in PVN than in AR but are not diagnostically specific\(^{15}\). Viral cytopathic changes are characteristic of PVN and identification of polyomavirus large T antigen (TAg) in renal tubular epithelial nuclei indicates active viral replication\(^{13,16,19}\).

Therapeutic or compliance-related reduction of immunosuppression (IS) significantly increases the risk of development of renal allograft rejection\(^{20,21}\). Allograft rejection in these circumstances may be a manifestation of immune recovery from cessation of IS therapy. One study of PVN in patients with resolving viremia after months of lowered IS has described the development of interstitial nephritis indistinguishable from Banff type 1 AR in serial follow-up biopsies\(^{3}\). Another study has reported increased severity of tubulitis in serial biopsies with PVN treated by reduced IS, and AR with endarteritis has been described in a patient who underwent reduction of IS therapy for PVN\(^{4,22}\). Together these studies suggest that reduction of IS, a widely used treatment of PVN, facilitates immune recovery in graft recipients and may increase the risk of graft rejection\(^{1,3,9,20}\). We have encountered 7 renal allograft biopsies with concurrent PVN and endarteritis over an 11-year period. Four arose after reduction of oral dosage of calcineurin inhibitors and discontinuation of mycophenolate maintenance immunosuppressive agents, and 3 arose without any apparent prior change of IS therapy.
the University of Chicago Institutional Review Board (IRB14-0052). Details tabulated included serum creatinine, urinary and blood BK polyomavirus (BKPyV) viral load, IS regimen, and changes in management preceding and following the index biopsy with concurrent disease. Graft loss was defined as a prolonged increase of serum creatinine to > 5 mg/dL or allograft nephrectomy. Measurements of BKPyV polymerase chain reaction (PCR) in urine were performed monthly for the first three months and then every three months for the first year and yearly thereafter. Patients with high-grade viremia (> 25 × 10^3 copies/mL) were then assessed for viremia. Quantitative PCR analysis for BKPyV was performed using the MagNA Pure LC DNA isolation kit (Roche Applied Science) and LightMix kit for the detection of polyomaviruses (Roche Applied Science). The BKPyV quantitative PCR assay is an institutionally developed multiplex assay that detects both BKPyV and JC polyomavirus (JCPyV) DNA. DNA extraction was performed using the MagNA Pure LC (Roche Diagnostic, Indianapolis, IN). A 219 bp fragment of the BKPyV and a 174 bp fragment of the JCPyV genome were amplified with specific primers and detected with probes labeled with LightCycler Red 705 (JCPyV) or with LightCycler Red 640 (BKPyV). An additional PCR product of 278 bp was formed from the internal positive control DNA (IPC) to verify the absence of amplification inhibitors in negative samples. The target is the gene for TAg. Primers and probes were purchased from TIB MOLBIOL, Berlin, Germany and were composed of the following: BKfor - acacgacgacgaagcag, BKrev - gggacgctggtaggtcc, JCfor - ctggaggaactcatcgtctga, JCrev - ggattcggtgatgataca, Anchor - ttttttcagaaaacattgctccagttgatagtaa, F - gcataaacgaagcctgagct, R - gcataaacgaagcctgccgtgagt, IPC SS - cactctatgaacctttaccacccacaccctccccc-PH, IPC F - atgacggtacaccgacccaa, IPC R - gcataaacgacagctcgtgagt, IPC SS - cactctatgaacctttaccacccacaccctccccc-PH, and IPC 705 LC 705 - cggatatgatgtcagcagctgccgtgagt-PH. Master mix was prepared using LightCycler FastStartPLUS DNA Master Hybridization Probes from Roche. The upper and lower limits of quantification of this PCR assay for BKPyV are 25 × 10^3 and 2.5 × 10^5 copies/mL, respectively.

RESULTS

Patient demographics
Between 2002 and 2012, 907 kidney transplants were performed at our institution. Of these, 94 developed PVN (10.4%) and 111 developed intimal arteritis (12.2%). Within this population, we observed 7 biopsies from 7 patients with concurrent PVN and endarteritis (7.4% of PVN cases, 6.3% of cases with intimal arteritis). The incidence of concurrent PVN and endarteritis was 0.8% in the kidney transplant population during the study period (approximately 60 times the expected frequency due to chance). All 7 recipients were male with a mean age of 48.3 years (range: 15-68 years). In comparison, there was a male:female ratio of 2.2 among patients with PVN (51 male, 23 female) as a whole and of 2.3 among all patients with intimal arteritis (77 male, 34 female), indicating a preponderance of males in our study population. All patients received transplants from deceased donors, with an average donor age of 31.4 years (range: 17-57 years). Following the transplant the mean baseline serum creatinine was 1.4 mg/dL (range: 1.1-1.8 mg/dL), although 1 biopsy was performed in the early transplant period before a stable serum creatinine was established. One patient had a simultaneous pancreas transplant. No patients had pretransplant donor specific antibodies (DSA). Patient demographics are depicted in Table 1.

Immunosuppressive therapy
Induction IS consisted of basiliximab in 6 patients and anti-thymocyte globulin (ATG) in 1 patient. Six patients were maintained on prednisone, tacrolimus and mycophenolate mofetil (MMF), and 1 patient was maintained on tacrolimus, sirolimus and prednisone (patient #7). Four patients had reduction of IS prior to the index biopsy, three for BK-related disease and one for pulmonary tuberculosis. For those with BK-related disease, two had biopsy-verified PVN, and one had BK viremia without confirmation of PVN on biopsy. MMF had been discontinued in 3 patients and tacrolimus dosage was reduced in 2 of the patients. Antiviral agents, leflunomide and cidofovir, were also given to these 3 patients. One patient also received 3 doses of pulsed steroids and 2 doses of intravenous immunoglobulin (IVIG) for pancreatic rejection that occurred 1 mo prior to the index kidney biopsy. Three patients had no known change of IS prior to the index biopsy. A detailed summary of IS for each patient is depicted in Table 2.

Clinical presentation
The mean serum creatinine was 2.7 mg/dL (range: 1.7-6.2 mg/dL) at the time of the index biopsy overall. The average time elapsed from transplantation to the index biopsy was 11.6 mo (range: 1.5-43.1 mo). The average time from reduction of IS to the index biopsy was 116 d (range: 21-236 d) for the patients who underwent reduced IS. Of note, patients with a reduction in IS prior to the index biopsy had higher average creatinine (3.3 mg/dL, range: 1.8-6.2 mg/dL) than those without (1.9 mg/dL, range: 1.7-2.2 mg/dL), had a higher frequency of diabetes mellitus (4/4 compared to 1/3) and higher donor age (38.5 years compared to 22.0 years). The clinical presentations are depicted in Table 2.

Histopathologic features
Biopsy specimens consisted of cortex only in 3 cases (43%) and both cortex and medulla in 4 (57%) cases. Index biopsies contained 23.2 glomeruli on average (range: 9-67). The average global glomerulosclerosis was 13.5% (range: 0%-70%). All cases demonstrated viral cytopathic effect and TAg expression by immunohistochemistry (Figure 1A). The average extent of TAg expression was 5.7% (range: 0.7%-11.5%, ICC = 0.8789). Endarteritis, with v1 lesions by Banff criteria,
was evident in all 7 cases (Figure 1B). Three cases in the group with reduced IS also had C4d staining of the peritubular capillaries, diffuse in 2 and focal in 1. One of these patients had negative assays for DSA around the time of the index biopsy, and 2 had no DSA data. Peritubular capillaritis was focal (Banff ptc score 0) and one had glomerulitis.

Two patients who had undergone IS reduction had prior biopsies showing PVN. Three of 4 patients who had undergone IS reduction developed graft loss. Index biopsies from allografts that subsequently underwent graft loss had diffuse tubulointerstitial inflammatory infiltrates (i + t score = 6) and abundant interstitial plasma cell infiltrates. Two of three had peritubular capillary C4d staining. A breakdown of the pathologic indices is given in Table 3.

Clinical course
Reduced oral maintenance IS was continued after the index biopsy for all patients with prior PVN or viremia (n = 3). Two of 3 patients received pulsed steroids either alone (n = 1) or with ATG (n = 1); another received IVIG without steroids. The recipient of IVIG had a stable serum creatinine at 155% of the baseline serum creatinine value at 12 mo follow up. The remaining 2 patients developed end-stage allograft failure due to rejection at 144 and 483 d after the index biopsy.

Table 1  Patient demographics

|                      | Known prior change of IS (n = 4) | No known prior change of IS (n = 3) | All cases (n = 7) |
|----------------------|---------------------------------|-----------------------------------|------------------|
| Age, years (range)   | 55.5 (43-68)                    | 38.7 (15-58)                      | 48.3 (15-68)     |
| Sex, n               | 4                               | 3                                 | 7                |
| Male                 |                                  |                                   |                  |
| Female               | 0                               | 0                                 | 0                |
| Cause of end stage renal disease, n |                    |                                   |                  |
| DM ± HTN             | 4                               | 1                                 | 5                |
| PCKD                 | 0                               | 1                                 | 1                |
| CON                  | 0                               | 1                                 | 1                |
| No. of HLA matches, average (range) |                     |                                   |                  |
| Class I (HLA-A, HLA-B) | 0.25 (0-1)                      | 0.33 (0-1)                        | 0.43 (0-2)       |
| Class II (HLA-DR)    | 0.50 (0-2)                      | 0.33 (0-1)                        | 0.43 (0-2)       |
| Cold ischemia time, hours (range) | 22.4 (15.0-37.5)                  | 17.8 (14.1-21.2)                  | 20.4 (14.1-37.5) |
| Delayed graft function, n | 1                               | 0                                 | 1                |
| Baseline creatinine, mg/dL (range) | 1.4 (1.1-1.8)                    | 1.6 (1.2-1.8)                     | 1.4 (1.1-1.8)    |
| Time of index biopsy, months after transplant (range) | 231 (135-317)                  | 507 (45-1293)                     | 349 (45-1293)    |
| Creatinine at index biopsy, mg/dL (range) | 3.3 (1.8-6.2)                    | 1.9 (1.7-2.2)                     | 2.7 (1.7-6.2)    |
| Donor-specific antibodies prior to transplant | 0                               | 0                                 | 0                |

HLA: Human leukocyte antigen; DM: Diabetes mellitus; HTN: Hypertension; PCKD: Polycystic kidney disease; CON: Congenital obstructive nephropathy; IS: Immunosuppression.
| BKV DNA copies/mL at index biopsy (× 10³ copies/mL) | BK viral trend (0–10) | Ulms (× 10¹⁹ copies/mL) | AR | Bcl2 | Bcl2 | TAg | TAg | Polyomavirus cytopathic changes | PVN | TAg expression combined with endarteritis in the same biopsy | TAg expression combined with endarteritis in the same biopsy | Concurrent PVN and rejection was associated with higher serum creatinine levels at time of the index biopsy, and higher Banff interstitial inflammation and tubulitis scores, compared to the group with no IS changes. Rejection, a likely consequence of immune recovery from reduced IS, demonstrated more severe patterns of tubulointerstitial inflammation and tubulitis.

**DISCUSSION**

This study describes the clinical and pathologic findings in a group of patients with compelling evidence of concurrent viral infection and rejection, as determined by polyomavirus cytopathic changes and TAg expression combined with endarteritis in the same biopsy. In 4 patients, rejection occurred after therapeutic reduction of calcineurin inhibitor dosage without any apparent change of IS therapy. These cases comprised 7.4% of allografts with PVN presenting over an 11-year period, and 0.8% of all kidney transplants over the same time period. Concurrent PVN and rejection in the setting of lowered IS was associated with higher serum creatinine levels at time of the index biopsy, and higher Banff interstitial inflammation and tubulitis scores, compared to the group with no IS changes. Rejection, a likely consequence of immune recovery from reduced IS, demonstrated more severe patterns of tubulointerstitial inflammation and tubulitis.

It is of interest that there were differences between PVN and AR arising with lowered IS and those arising spontaneously without change of IS regimes. PVN and AR differed in that the former were associated with higher serum creatinine levels at time of the index biopsy, and higher Banff interstitial inflammation and tubulitis scores, compared to the group with no IS changes. Rejection, a likely consequence of immune recovery from reduced IS, demonstrated more severe patterns of tubulointerstitial inflammation and tubulitis.

**Table 2: Clinical information**

| Baseline Cr | Serum Cr at index biopsy (mg/dL) | BK viral trend (0–10) | Ulms (× 10¹⁹ copies/mL) | AR | Bcl2 | Bcl2 | TAg | TAg | Polyomavirus cytopathic changes | PVN | TAg expression combined with endarteritis in the same biopsy | TAg expression combined with endarteritis in the same biopsy | Concurrent PVN and rejection was associated with higher serum creatinine levels at time of the index biopsy, and higher Banff interstitial inflammation and tubulitis scores, compared to the group with no IS changes. Rejection, a likely consequence of immune recovery from reduced IS, demonstrated more severe patterns of tubulointerstitial inflammation and tubulitis.

**Discussion**

This study describes the clinical and pathologic findings in a group of patients with compelling evidence of concurrent viral infection and rejection, as determined by polyomavirus cytopathic changes and TAg expression combined with endarteritis in the same biopsy. In 4 patients, rejection occurred after therapeutic reduction of calcineurin inhibitor dosage without any apparent change of IS therapy. These cases comprised 7.4% of allografts with PVN presenting over an 11-year period, and 0.8% of all kidney transplants over the same time period. Concurrent PVN and rejection in the setting of lowered IS was associated with higher serum creatinine levels at time of the index biopsy, and higher Banff interstitial inflammation and tubulitis scores, compared to the group with no IS changes. Rejection, a likely consequence of immune recovery from reduced IS, demonstrated more severe patterns of tubulointerstitial inflammation and tubulitis.
Serum creatinine values are interpreted as lesions of recent onset. Sites of PV infection were accompanied by interstitial fibrosis and tubular atrophy indicative of a chronic inflammatory lesion that we strongly suspect predated the lesions of tubular atrophy indicative of a chronic inflammatory lesion. It is thus possible that these cases are also interpretable as lesions of recent onset. Sites of PV infection were accompanied by interstitial fibrosis and tubular atrophy indicative of a chronic inflammatory lesion that we strongly suspect predated the lesions of rejection. It is thus possible that these cases are also examples of rejection superimposed on PV infection. Renal dysfunction and rejection was milder and each had a good outcome. Two patients were treated with antirejection therapy that may have helped stabilize graft function. One was treated by reduction of maintenance IS without antirejection therapy and had graft dysfunction for more than 6 mo after diagnosis, with eventual return of creatinine levels to baseline and clearance of viremia similar to the patients described by Menter et al[3], even though their patients only had tubulointerstitial and not arterial inflammation. Our three patients had stable graft function, at < 110% of baseline creatinine, with clearance of viremia by 9 mo of follow up, and no evidence of rejection in follow-up biopsies. Although trends from this small and somewhat heterogeneous group of patients must be interpreted with caution, our observations suggest that renal allografts with PVN and endarteritis arising with reduced IS may potentially have more severe rejection and be at greater risk of allograft loss from rejection.

This small series clearly shows that AR may arise during the course of PVN treated by reduced IS, and perhaps surprisingly, that these lesions may present simultaneously without such a change in treatment. Concurrent PVN and AR also appears to be more frequent than currently appreciated in the literature, as these findings were evident in 7.4% of allografts performed in the study period.

### COMMENTS

#### Background

Kidney transplants are at constant risk of acute rejection (AR) for which recipients receive immunosuppression (IS). IS increases the risk of infection. Here the authors report the concurrence of both polyomavirus infection and rejection-associated endarteritis in renal allografts and describe the clinical and pathologic features of these lesions.

#### Research frontiers

Both polyomavirus nephropathy (PVN) and AR are characterized by tubulointerstitial inflammation and distinction of these processes, although essential, is difficult. Endarteritis is pathognomonic of AR and its identification in the context of PVN indicates that both AR and viral infection are present in the allograft.

#### Innovations and breakthroughs

Concurrent AR and polyomavirus infection is not well characterized in renal allografts. This biopsy series has diagnostic features of both processes allowing observation of the clinical course of allografts with these lesions.
Applications
Concurrent polyomavirus infection and endarteritis arose in 7.4% of our patients with PVN, suggesting a higher frequency than is currently appreciated. The authors also noted that when endarteritis arose after reduction of IS, graft loss from rejection occurred in 3 of 4 patients. Three of 3 allograft recipients with simultaneous PVN and endarteritis had stable function at 1 year follow up.

Terminology
Endarteritis is arterial intimal monocellular inflammation found specifically in acute rejection. Polyomavirus nephropathy is viral infection of the allograft manifested by cytotoxic changes in tubular epithelium, detectable large T antigen by immunohistochemistry, viremia and viruria.

Peer-review
The manuscript by McGregor et al studies the concurrency between polyomavirus nephropathy and endarteritis in 94 kidney transplant patients. They found 7 patients (all male) that developed both PVN and endarteritis. In four of them endarteritis arose after reduction of immunosuppression, and three of them lost their grafts. Patients that got PVN and endarteritis after lowered immunosuppression had high serum creatinine levels and Banff interstitial inflammation and tubulitis scores.

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