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Renal allograft granulomatous interstitial nephritis: observations of an uncommon injury pattern in 22 transplant recipients

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Abstract

Background: Granulomatous interstitial nephritis (GIN) is uncommon in native kidneys, and descriptions in allografts are few. We report clinical and pathologic findings in 22 allograft recipients with GIN identified in renal allograft biopsies and nephrectomies.

Methods: Renal allografts with GIN were retrieved from the pathology files of two academic medical centers. Available clinical and pathologic data were compiled retrospectively for a 23-year period.

Results: GIN was present in 23 specimens from 22 patients (15 males and 7 females) with allograft dysfunction [serum creatinine averaged 3.3 mg/dL (range 1.4–7.8)], at a mean age of 48 years (range 22–77). GIN was identified in 0.3% of biopsies at a mean of 552 days post transplantation (range 10–5898). GIN was due to viral (5), bacterial (5) and fungal (2) infections in 12 (54.5%), and drug exposure was the likely cause in 5 cases (22.7%). One had recurrent granulomatosis with polyangiitis. In 4 cases, no firm etiology of GIN was established. Of 18 patients with follow up data, 33.3% had a complete response to therapy, 44.5% had a partial response and 22.2% developed graft loss due to fungal and E. coli infections. All responders had graft survival for more than 1 year after diagnosis of GIN.

Conclusions: Allograft GIN is associated with a spectrum of etiologic agents and was identified in 0.3% of biopsies. Graft failure occurred in 22% of this series, due to fungal and bacterial GIN; however, most had complete or partial dysfunction reversal and long-term graft survival after appropriate therapy.

Key words: histopathology, kidney, nephritis, transplant, urinary tract infection

Introduction

Granulomatous inflammation is a distinctive reaction of cells of the monocyte-macrophage lineage to multiple injurious agents. Granuloma formation may occur in the absence of adaptive immunity by innate immune mechanisms [1]. Acquired immunity enhances the effector function of granulomas mainly
Renal allograft granulomatous inflammation

Table 1. Reports of allograft GIN

<table>
<thead>
<tr>
<th>N</th>
<th>Details</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>22</td>
<td>• Infection (n = 12) [adenovirus (n = 3), polymavirus (n = 2), Mycobacteria (n = 2), C. albicans (n = 1), C. neoformans (n = 1) and bacterial UTI (n = 3)]</td>
<td>Current paper</td>
</tr>
<tr>
<td></td>
<td>• Drug (n = 5 cases) [bactrim (n = 3), dapsone (n = 1) and foscarnet (n = 1)]</td>
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</tr>
<tr>
<td></td>
<td>• Recurrent granulomatosis with polyangiitis (n = 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Unknown (n = 4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>• Infection (M. tuberculosis)</td>
<td>al-Sulaiman 1990 [15]</td>
</tr>
<tr>
<td>3</td>
<td>• Drug or UTI (n = 1)</td>
<td>Hotta 2012 [7]</td>
</tr>
<tr>
<td>3</td>
<td>• Idiopathic (n = 2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>• Recurrent sarcoidosis</td>
<td>Aouizerate 2010 [33]</td>
</tr>
<tr>
<td>3</td>
<td>• Infection [histoplasma (n = 1)]</td>
<td>Lapasia 2010 [43]</td>
</tr>
<tr>
<td></td>
<td>• Drug (n = 1)</td>
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</tr>
<tr>
<td></td>
<td>• Idiopathic (n = 1)</td>
<td></td>
</tr>
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<td>• Infection (M. tuberculosis)</td>
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</tr>
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<td>Ozdemir 2006 [19]</td>
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<td>Goncalves 1992 [14]</td>
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<td>• Recurrent tubulointerstitial nephritis and uveitis syndrome</td>
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<td>Hobbs 2009 [34]</td>
</tr>
<tr>
<td>1</td>
<td>• Infection (coccidioidomycosis)</td>
<td>Baden 2009 [44]</td>
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<td>Alsaad 2007 [23]</td>
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<td>1</td>
<td>• Infection (Pseudomonas aeruginosa)</td>
<td>Koike 2007 [45]</td>
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<tr>
<td>1</td>
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<td>Mahmood 2004 [46]</td>
</tr>
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<td>1</td>
<td>• Sarcoi dosis</td>
<td>Kukura 2004 [33]</td>
</tr>
<tr>
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<td>• Infection (Rhodococcus)</td>
<td>Tse 2004 [21]</td>
</tr>
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<td>1</td>
<td>• Infection (adenovirus)</td>
<td>Asim 2003 [22]</td>
</tr>
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<td>1</td>
<td>• Drug (bactrim)</td>
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<td>Napathorn 1996 [8]</td>
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<tr>
<td>1</td>
<td>• Sarcoi dosis</td>
<td>Shen 1986 [28]</td>
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<tr>
<td>63 total</td>
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</table>

UTI, urinary tract infection.

Fig. 1. Pie chart depicting the number of patients comprising different diagnostic categories based on the literature reviewed. GPA, recurrent granulomatosis with polyangiitis; TINU, recurrent tubulointerstitial nephritis and uveitis syndrome.

by T cell activation [2]. Involvement of the kidney is most commonly manifested by granulomatous interstitial nephritis (GIN); however, both granulomatous glomerulonephritis and vasculitis are also described [3]. GIN is a distinct pattern of inflammation occurring in up to 0.9% of native renal biopsies [4] and up to 5.9% of native biopsies with tubulointerstitial nephritis [5]. Consistent with the initial innate nature of granulomatous inflammation, the capacity to form granulomas is retained in immune deficiency states [1] and is also rarely described in renal allografts [6–9].

Interstitial inflammation in renal allografts is most frequently caused by acute cellular rejection (ACR), and macrophages are a prominent component of these interstitial infiltrates [10, 11]. Macrophages in ACR tend to have an infiltrative pattern, and the presence of nodules or discrete aggregates of epithelioid macrophages raises diagnostic consideration of allograft interstitial nephritis from causes other than rejection. Prior reports of allograft GIN have attributed the etiology to bacterial and fungal infections [6, 7] and sarcoidosis [12]. Drug toxicity or hypersensitivity, mycobacterial infections [9, 13–19], other bacterial urinary tract pathogens [9, 20, 21], adenovirus [22–26] and fungal infections [19, 27] have documented associations with native GIN. GIN may theoretically arise as a de novo event in the allograft from any of the etiologic agents that cause GIN in native kidneys. Recurrent disease related to sarcoidosis [12, 28–34] or tubulointerstitial nephritis and uveitis (TINU) syndrome [35], are also diagnostic considerations. Rates of graft failure in GIN are highest in Mycobacterium tuberculosis infection [6, 8, 9, 14, 15, 19, 36] with more than 80% graft loss, in contrast to GIN associated with other infections and non-infectious GIN, where graft survival with or without impairment of function, is frequently observed (references in Table 1 and Figure 1 and [37–39]). The relative rarity of renal allograft GIN led us to combine data from two academic renal transplant centers to analyze etiologic and morphologic features of a relatively large cohort observed over a period of 23 years.

Materials and methods

Allograft GIN cases were retrieved from the pathology information systems of two academic medical centers. One additional case of GIN was contributed from an outside institution by one of the authors (S.M.M.). This investigations in this study received Institutional Review Board approval. GIN inclusion criteria required at least one circumscribed aggregate of epithelioid macrophages with or without giant cells in the tubulointerstitial...
compartment. Serial sections were used to assess the extent of granulomatous inflammation. All biopsies had at least 12 serial sections evaluated using hematoxylin and eosin (H&E) and periodic acid–Schiff (PAS) stains. Multiple blocks of the one nephrectomy specimen were evaluated using H&E and PAS sections also. Furthermore, trichrome and Jones silver stains were often performed; and a periodic acid silver methenamine stain was performed in some cases. Clinical and pathologic data were compiled retrospectively. Complete response (CR) to therapy was defined as return of the serum creatinine value to within 10% of the baseline value after therapy. Partial response (PR) was defined as return of the serum creatinine value to between 11 and 50% of the baseline value after therapy.

The biopsies and the nephrectomy specimens were examined using standard H&E and PAS stains. Ancillary studies utilized in most cases included histochemical staining for acid-fast bacilli by standard Ziehl-Neelsen, and for fungal microorganisms by standard Grocott methenamine silver and PAS methods. These stains were not performed in cases of adenovirus and polyomavirus nephropathy where granulomas surrounded tubules with viral cytopathic changes. Standard immunohistochemistry for adenovirus (monoclonal clone: 20/11; titration: 1:400; EMD Millipore, Temecula, CA, USA) and the SV40 large T polyomavirus antigen (monoclonal clone: PAB416; titration: 1:400; Oncogene Research, San Diego, CA, USA) was also performed when indicated by the light microscopic or clinical findings. Histologic evaluation of allograft tissues was performed by three observers (A.B.F., C.L.E., S.M.M.) to determine the following: (i) granuloma distribution, size, shape, number, necrosis and microorganisms; (ii) tubulointerstitial lymphoid, neutrophil, eosinophil and plasma cell infiltrates; (iii) Raniff indices [40]; (iv) C4d status; and (v) any additional pathology. Granuloma size was arbitrarily compared with glomerular size and was graded as less than, equal to or greater than the glomerular diameter.

Immunofluorescence or immunohistochemistry for C4d was performed in 15 cases. One had direct immunofluorescence performed for IgG, IgA, IgM, C3, kappa and lambda light chains and revealed nonspecific findings only. Electron microscopic studies were not performed.

Statistical analysis

Statistical analysis was performed in Microsoft Excel, SAS JMP version 10.0 (SAS Institute, Cary, NC, USA). Group comparisons were analyzed using nonparametric methods including Mann-Whitney U test, Chi square and Fisher exact tests. A P-value <0.05 was accepted as significant, adjusted using the Bonferroni method for multiple comparisons [41].

Results

Clinical features (Table 2)

Evidence of allograft infection was present in 12 cases (54.5%). Eight tissue specimens had direct evidence of the infectious agents in histologic sections (34.8% of total, 67% of infectious GIN). GIN attributable to adenovirus (n = 3) and polyomavirus (n = 2) had viral cytopathic changes and detectable viral antigens by immunohistochemistry (Figure 2), and the tubular profiles with detectable viral antigens were frequently localized within granulomas. Acid-fast mycobacterial bacilli (n = 1), Candida albicans (n = 1), and Cryptococcus neoformans (n = 1) were observed within granulomas in tissue sections using ancillary histochemical stains (Figure 3). Persistent or recurrent bacterial urinary tract infections with features of megalocytic interstitial nephritis (MIN) (n = 3) were attributable to Escherichia coli infection in two (Figure 4) and Klebsiella pneumoniae in one. These biopsies had extensive tubular destruction, tubular basement membrane rupture and PAS-positive macrophages, possibly related to ascending urinary infection. Malakoplakia was excluded by the absence of Michaelis-Gutmann bodies. One biopsy had multiple small glomerular and tubulointerstitial granulomas, including focal glomerular necrosis, with evidence of miliary M. tuberculosis infection on chest X-ray, acid fast bacilli in bronchoalveolar lavage and on transbronchial biopsy. No microorganisms were identified in the allograft biopsy.

Drug hypersensitivity was the likely etiology in five cases (22.7%) as determined by clinicopathological correlation. Pharmacologic agents implicated included bacitracin (n = 2), dapsone (n = 1), fosfomycin (n = 1), and bactrim or omeprazole or acyclovir (n = 1). A decrease in the serum creatinine level after cessation of exposure to the suspected agent confirmed the clinical suspicion of drug-induced disease. No crystal deposits, no calcifications and no asteroid bodies were observed. One patient had recurrent granulomatosis with polyangiitis (GPA) on post-transplant day 11, with granulomatous arteritis (Figure 5) but no glomerular crescents. In four cases, no firm etiology of GIN could be established, mainly because of lack of available retrospective clinical and laboratory data. In two of these cases, acid-fast bacterial and fungal stains were negative, and urine cultures were also negative. In the third case, fungal stains were negative. For the
sixth case, acid fast bacterial and fungal stains were not performed and urine cultures were not available; however, the suspicion of an infection on histologic examination was quite low since there was no necrosis or giant cells. Overall, for these cases, a drug reaction was felt to be the most likely etiology and hence these are categorized as non-infectious.

For comparative purposes we subdivided the biopsies into infectious (13 tissue samples from 12 patients) and noninfectious GIN (10 biopsies from 10 patients) groups. Identification of microorganisms in tissue sections, megacystic patterns of GIN and granulomatous granulomas were exclusive to the infectious GIN group. None of the other comparative histologic findings met Bonferroni-adjusted P-values of significance (Table 3). Necrosis in granulomas was infrequent (6 of 23 tissue samples), and was observed in the context of infections due to adenovirus (n = 2), mycobacteria (one with caseous necrosis and one with granulomatous necrosis) and E. coli (one with central suppurative necrosis), and one GIN of undetermined cause.

The Banff allograft inflammatory indices [44–46] were not significantly different between the groups. Six of 13 in the infectious GIN group and 4 of 10 in the noninfectious group had tubulointerstitial infiltrates meeting criteria for type I rejection by the Banff criteria [45]. Endarteritis was seen in two samples from the infectious GIN group, and in two of the noninfectious group, one of which also had granulomatous arteritis and was considered a manifestation of recurrent GPA. One example of GIN of unknown etiology had transmural arteritis and peritubular capillary C4d deposition suspicious for antibody-mediated rejection. The donor-specific antibody status of the patient is unknown.

### Follow-up (Table 4)

Follow-up information was available for 18 patients, with notable differences in outcome between infectious (n = 12) and noninfectious (n = 6) groups.

Six patients had a CR to therapy (one infectious and five noninfectious GIN). Causative agents were thought to be drugs (bactrim n = 2, fosfamet n = 1), recurrent GPA (n = 1), polyomavirus (n = 1) and unknown (n = 1). Each biopsy had three or fewer, small granulomas, and the biopsies were obtained earlier in the posttransplantation period [mean 128 days, compared with 310 days in the PR and 518 days in the graft loss (GL) groups]. The interstitial fibrosis and tubular atrophy scores were lower in CR (0.6 vs 2.1 in PR and 2.8 in GL, but not significantly P = 0.078).

Eight patients had a PR to therapy (seven infectious and one noninfectious GIN). Infections included adenovirus (n = 3), polyomavirus (n = 1), M. tuberculosis (n = 2) and K. pneumoniae (n = 1). One drug-induced GIN was related to exposure to dapsone. Four partial responders had multiple cortical and medullary granulomas related to adenovirus (n = 2) and mycobacterial infection (n = 2), and four had few, mainly cortical granulomas related to infection (polyomavirus n = 1, adenovirus n = 1, K. pneumoniae n = 1) and drug-induced GIN (dapsone n = 1).

One patient died from systemic C. albicans and respiratory syncytial virus infections, 2 days after the index biopsy at day 32, and 1 day after nephrectomy. A patient with disseminated C. neoformans infection had an allograft nephrectomy on posttransplant day 513. The nephrectomy had abundant cortical and medullary granulomas with budding spores of C. neoformans and active and chronic rejection features with microvascular inflammation (glomerulitis and peritubular capillaritis), transplant glomerulopathy and endarteritis with chronic transplant arteriopathy. Two additional graft losses were attributable to diffuse severe granulomatous inflammation arising in the context of persistent or recurrent E. coli urinary infection and MIN. No allograft recipients in the noninfectious group had graft loss in more than 1 year of follow-up after the index biopsy.

The frequency of qualitative features of granulomas (location, tubulocentricity, necrosis, giant cells), other inflammatory
cell types, and Banff indices of graft inflammation and fibrosis, did not differ between the CR, PR and GL groups. Inflammatory infiltrates meeting criteria for borderline infiltrates or acute T-cell-mediated rejection, type I, by Banff criteria [45], were present in 67% of CR, 88% of PR and 25% of GL groups. Endarteritis was present in 17%, 12.5% and 50% of these allografts, respectively. Withdrawal or reduction of immunosuppressive medications preceded development of endarteritis in the GL cases. Only one example of endarteritis was observed in each of the CR and PR groups.

Discussion

Our observations in this retrospective study of 22 allograft recipients suggest that allograft GIN is relatively uncommon at 0.3% of renal allograft biopsies from cohorts at two institutions. GIN occurs in native kidneys with a frequency of 0.47–0.9% of biopsies [4, 42], so it would appear that allografts are not at greater risk of GIN. Biopsy estimates of the frequency of GIN depend on many factors including the frequency and distribution of kidney involvement in a granulomatous disease, the clinical threshold and indications for biopsy, biopsy sampling error and interpretation, all of which probably contribute to underestimation of the true frequency of kidney involvement by this process. Our study is limited by retrospective analysis, absence of some clinical data and relatively small subgroup sizes, a common problem in the study of diseases.

Infection was responsible for GIN in 54.5% of our cohort, with the remainder thought to be unrelated to infection, although data for a thorough evaluation of etiology was absent in four patients. Infection is the most common reported cause of allograft GIN, accounting for 63.9% of reported cases [6–9, 14, 15, 19, 21, 22, 24–26, 36, 43–45]. Mycobacterium tuberculosis is the single most commonly reported agent associated with allograft GIN at 39% of reported cases [6, 8, 9, 14, 15, 19, 36]. We identified M. tuberculosis in only 9.1% of our biopsies. The frequency of adenovirus and Gram-negative bacterial infections were comparable in frequency to the reported cases (about 14% for each infection). Reported series of native kidney biopsies with GIN have a frequency of infectious causes of only 18% [4, 5]. Drug-induced GIN was observed in 22.7% of our series, a frequency much higher than the reported frequency of 2.8% in allograft

Table 3. Summary of histologic findings in allograft GIN

<table>
<thead>
<tr>
<th></th>
<th>Infectious</th>
<th>Noninfectious</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Tissue specimens</td>
<td>13</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Biopsy time in days (median, range)</td>
<td>195 (33–1416)</td>
<td>18 (10–5998)</td>
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</tr>
<tr>
<td>Granulomas</td>
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<tr>
<td>Cortex + medulla</td>
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<tr>
<td>Cortex only</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Medulla only</td>
<td>2</td>
<td>2</td>
<td>0.42</td>
</tr>
<tr>
<td>Few*</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Many</td>
<td>9</td>
<td>3</td>
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<tr>
<td>Confluent sheets</td>
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<tr>
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<td>11</td>
<td>3</td>
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<tr>
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<td>6</td>
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</tr>
<tr>
<td>Necrosis</td>
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<tr>
<td>Giant cells</td>
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<tr>
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<tr>
<td>Microorganisms</td>
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<tr>
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<tr>
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<tr>
<td>t</td>
<td>1.9</td>
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<td>i2t2 or more</td>
<td>6</td>
<td>4</td>
<td>1</td>
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<tr>
<td>g</td>
<td>0.15</td>
<td>0.3</td>
<td>0.6</td>
</tr>
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<td>ptc</td>
<td>0.08</td>
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<tr>
<td>v</td>
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<td>1/7</td>
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<td>Other findings</td>
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<tr>
<td>Thrombotic microangiopathy</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Immune complex GN</td>
<td>0</td>
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<td>–</td>
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GN, glomerulonephritis; IN, interstitial nephritis; PTC, peritubular capillary.

* few – three or fewer
GIN [6–9, 12, 14, 15, 19, 21–26, 28, 31–36, 43–47]. The low frequency of drug-induced GIN in renal allografts contrasts with studies of native kidneys, where drug exposure accounts for 36% of reported cases and is the most common cause of GIN [4, 5, 42, 48, 49].

Granulomatous inflammation has been observed in up to 15% of allograft biopsies with polyomavirus nephropathy (PVN), and intratubular granulomas have also been described in this setting [50]. In our experience, granulomatous inflammation is an uncommon feature of PVN, and only two examples were observed over many years in the current study. GIN is also an unusual feature of bacterial infection, most often described in the context of immunosuppression, and manifest histologically as MIN or malakoplakia [51]. We identified three examples of MIN resulting in severe graft injury, with extensive destructive granulomatous inflammation, related to chronic persistent or recurrent urinary E. coli and K. pneumoniae infections. Each of these patients had been exposed to antibiotics that could potentially cause GIN, and hence a contribution of drug hypersensitivity cannot be entirely excluded, a conundrum noted by others in transplanted [6, 7] and native kidneys [5, 20]. Graft loss was observed in two cases of MIN associated with persistent or recurrent E. coli infection occurring long after cessation of exposure to potentially offending pharmacologic agents.

Infection-related allograft GIN had some distinctive morphologic features including microorganisms in granulomas, megakaryocytic inflammation and glomerular granulomas in the setting of miliary tuberculosis, none of which was seen in noninfectious GIN. There were no other qualitative differences in the distribution, the type of granuloma (necrotizing vs nonnecrotizing), giant cells, granulocytic and plasmacytic infiltrates, and Banff inflammatory indices between the etiologic groups. GIN has a wide variety of etiologic associations, which occasionally present direct evidence of their nature in biopsies. Infectious microorganisms, crystals and clefts, and vasculitic glomerulonephritis may provide diagnostic clues to the underlying etiology of GIN. In the absence of these diagnostic clues, GIN is a nonspecific pattern of renal injury requiring careful clinical and pathologic correlation for final diagnosis.

Tubulointerstitial mononuclear infiltrates meeting criteria for borderline and type IA or IB T cell ACR by Banff criteria [45], were frequently observed in GIN with or without infection. Five patients had GIN and endarteritis, two of which occurred after reduction or cessation of immunosuppression for management of infection, prior to allograft loss. One was associated with recurrent GPA. One of two cases with follow up was treated for acute rejection and had a PR. Despite meeting criteria for
rejection it seems plausible that tubulointerstitial mononuclear infiltrates in allografts could be related to GIN, as such infiltrates are seen in native kidney biopsies with GIN [4, 5, 42]. The presence of endarteritis, however, indicates that concurrent but distinct processes of GIN and rejection can be observed simultaneously. Concurrency of rejection and other pathologic processes, including GIN, has been observed in allograft infections [50, 52], and may reflect a state of reduced immunosuppression predisposing to rejection, or perhaps graft inflammation, or its etiologic stimulus, indirectly amplifies graft immunogenicity and triggers a rejection response. An ‘Occam’s razor’-type approach is typically taken with the diagnosis of rejection, and other causes of graft inflammation are excluded before a diagnosis is made [40].

Subdivision of the groups by etiology and outcome revealed that complete responders to therapy typically had noninfectious GIN with three or fewer small granulomas and lower Banff ci and ct scores in biopsies obtained within the first 6 months after transplantation. Active GIN of limited extent and with limited chronic changes may be reversible with appropriate therapy. In our cohort, a minority of the patients developed graft failure (22%); and most had a partial or complete recovery of graft function, on follow up of over 1 year. Complete responses of allograft function occurred almost exclusively in noninfectious GIN. Graft loss and partial recovery of function occurred almost exclusively in infectious GIN. This finding emphasizes the importance of close clinicopathologic correlation and utilization of ancillary studies for correct diagnosis, since, not surprisingly, the outcome appears to be dependent on the underlying etiology. Our experience suggests that the prognosis of allograft GIN may be better than expected from the literature with high rates of graft failure reported in infectious GIN, especially in M. tuberculosis infection [6, 8, 9, 14, 15, 19, 36], and better than in native GIN [4, 53], as more than three-quarters of our patients had a favorable outcome with long-term graft survival.

Table 4. Outcome

<table>
<thead>
<tr>
<th>Treatment response</th>
<th>Infectious</th>
<th>Noninfectious</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Graft loss</td>
<td>4</td>
<td>0</td>
<td>0.006</td>
</tr>
<tr>
<td>No data</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

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Authors’ contributions

Research idea and study design: A.B.F., S.M.; data acquisition: A.B.F., C.L.E., S.M., W.J.C., A.C.; data analysis/interpretation: A.B.F., C.L.E., S.M.; statistical analysis: A.B.F., S.M.; supervision or mentorship: A.B.F., S.M. All authors contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. A.B.F. takes responsibility for the fact that this study has been reported honestly, accurately and transparently, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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