



## ORIGINAL ARTICLE

# 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

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Table 1. Reports of allograft GIN

N	Details	Reference
22	<ul style="list-style-type: none"> <li>• Infection (n = 12) [adenovirus (n = 3), polyomavirus (n = 2), <i>Mycobacteria</i> (n = 2), <i>C. albicans</i> (n = 1), <i>C. neoformans</i> (n = 1) and bacterial UTI (n = 3)]</li> <li>• Drug (n = 5 cases) [bactrim (n = 3), dapsone (n = 1) and foscarnet (n = 1)]</li> <li>• Recurrent granulomatosis with polyangiitis (n = 1)</li> <li>• Unknown (n = 4)</li> </ul>	Current paper
4	<ul style="list-style-type: none"> <li>• Infection (<i>M. tuberculosis</i>)</li> </ul>	al-Sulaiman 1990 [15]
3	<ul style="list-style-type: none"> <li>• Drug or UTI (n = 1)</li> <li>• Idiopathic (n = 2)</li> </ul>	Hotta 2012 [7]
3	<ul style="list-style-type: none"> <li>• Recurrent sarcoidosis</li> </ul>	Aouizerate 2010 [33]
3	<ul style="list-style-type: none"> <li>• Infection [<i>Histoplasma</i> (n = 1)]</li> <li>• Drug (n = 1)</li> <li>• Idiopathic (n = 1)</li> </ul>	Lapasias 2010 [43]
3	<ul style="list-style-type: none"> <li>• Infection (<i>M. tuberculosis</i>)</li> </ul>	Khaira 2009 [36]
3	<ul style="list-style-type: none"> <li>• Infection [<i>M. tuberculosis</i> (n = 2) and <i>C. albicans</i> (n = 1)]</li> </ul>	Ozdemir 2006 [19]
3	<ul style="list-style-type: none"> <li>• Infection (<i>M. tuberculosis</i>)</li> </ul>	Goncalves 1992 [14]
2	<ul style="list-style-type: none"> <li>• Infection [<i>M. tuberculosis</i> (n = 1), <i>Klebsiella</i> UTI (n = 1)]</li> </ul>	Gupta 2014 [9]
1	<ul style="list-style-type: none"> <li>• Infection (adenovirus)</li> </ul>	Lachiewicz 2014 [24]
1	<ul style="list-style-type: none"> <li>• Recurrent sarcoidosis</li> </ul>	Bagnasco 2014 [12]
1	<ul style="list-style-type: none"> <li>• Infection (adenovirus)</li> </ul>	Parasuraman 2013 [25]
1	<ul style="list-style-type: none"> <li>• Recurrent tubulointerstitial nephritis and uveitis syndrome</li> </ul>	Onyekpe 2011 [35]
1	<ul style="list-style-type: none"> <li>• Infection (Adenovirus)</li> </ul>	Storsley 2011 [26]
1	<ul style="list-style-type: none"> <li>• Sarcoidosis</li> </ul>	Vargas 2010 [32]
1	<ul style="list-style-type: none"> <li>• Sarcoidosis</li> </ul>	Hobbs 2009 [34]
1	<ul style="list-style-type: none"> <li>• Infection (coccidioidomycosis)</li> </ul>	Baden 2009 [44]
1	<ul style="list-style-type: none"> <li>• Infection (adenovirus)</li> </ul>	Alsaad 2007 [23]
1	<ul style="list-style-type: none"> <li>• Infection (<i>Pseudomonas aeruginosa</i>)</li> </ul>	Koike 2007 [45]
1	<ul style="list-style-type: none"> <li>• ACR with tubular rupture</li> </ul>	Mahmood 2004 [46]
1	<ul style="list-style-type: none"> <li>• Sarcoidosis</li> </ul>	Kukura 2004 [31]
1	<ul style="list-style-type: none"> <li>• Infection (<i>Rhodococcus</i>)</li> </ul>	Tse 2004 [21]
1	<ul style="list-style-type: none"> <li>• Infection (adenovirus)</li> </ul>	Asim 2003 [22]
1	<ul style="list-style-type: none"> <li>• Drug (bactrim)</li> </ul>	Josephson 1999 [47]
1	<ul style="list-style-type: none"> <li>• Infection (<i>M. tuberculosis</i>)</li> </ul>	Napathorn 1996 [8]
1	<ul style="list-style-type: none"> <li>• Sarcoidosis</li> </ul>	Shen 1986 [28]
63 total		

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

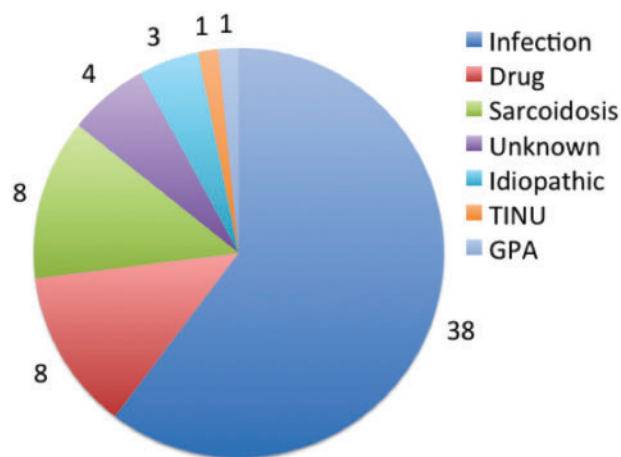


Fig. 1. Pie chart depicting the number of patients comprising different diagnostic categories based on the literature reviewed. GPA, recurrent granulomatosis with polyangiitis; TINU, recurrent tubulointerstitial nephritis and uveitis syndrome

compartment. Serial sections were used to assess the extent of granulomatous inflammation. All biopsies had a 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. Available 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) Banff 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)

GIN was present in 23 renal allograft tissue specimens from 22 patients obtained over a 23-year period. Twenty-one biopsy specimens from 20 patients were identified among approximately 7000 kidney transplant biopsies from two centers during the observation period, for a prevalence of 0.3%. One institution had a frequency of 0.53% and the second 0.2%. One additional biopsy was from an outside institution. One specimen had GIN identified in an allograft nephrectomy. The allograft recipients consisted of 15 males and 7 females with a mean age of 48.3 years (standard deviation = 17, range = 22–77 years). There were 10 African Americans, 6 Caucasians, 2 Hispanic and 1 Asian; race was unknown in three cases. GIN was identified at a mean of 552 days post-transplant (median = 176, range = 10–5898 days). The serum creatinine averaged 3.3 mg/dL (range = 1.4–7.8) at the time of diagnosis.

### Pathologic features (Table 3)

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 bactrim ( $n=2$ ), dapsone ( $n=1$ ), foscarnet ( $n=1$ ), 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

Table 2. Demographic and clinical data

Age (mean, range), years		48.3	22–77
Gender		7F:15M	
Race	Black	10	
	White	6	
	Latino	2	
	Asian	1	
	Unknown	3	
Primary disease	Diabetic nephropathy	3	
	Hypertension	5	
	Diabetic nephropathy and hypertension	1	
	Autosomal dominant polycystic kidney disease	2	
	Lupus nephritis	1	
	Granulomatosis with polyangiitis	1	
	Chronic GN	3	
	AA amyloid	1	
	Unknown	5	
Baseline Cr (mean, range), in mg/dL <sup>a</sup>		1.72	0.9–3
Cr at biopsy (mean, range), in mg/dL <sup>a</sup>		3.3	1.4–7.8
Immunosuppression	Prednisone, mycophenolate, tacrolimus	12	
	Prednisone, mycophenolate, sirolimus	1	
	Prednisone, tacrolimus	1	
	Prednisone, azathioprine, cyclosporine	2	
	Mycophenolate, tacrolimus	1	
	Belatacept, prednisone, mycophenolate	1	
Unknown	4		

Cr, creatinine; F, female; GN, glomerulonephritis; M, male.

<sup>a</sup> Conversion factor for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ .

fourth case, acid fast bacterial and fungal stains were not performed and urine cultures are 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 four 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 GIN (13 tissue samples from 12 patients) and noninfectious GIN (10 biopsies from 10 patients) groups. Identification of microorganisms in tissue sections, megalocytic patterns of GIN and glomerular 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 glomerular 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  $n=2$ , foscarnet  $n=1$ ), 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

Table 3. Summary of histologic findings in allograft GIN

	Infectious	Noninfectious	p
Patients	12	10	
Tissue specimens	13	10	
Biopsy time in days (median, range)	195 (33–1416)	18 (10–5998)	0.08
Granulomas			
Cortex + medulla	6	2	
Cortex only	5	6	
Medulla only	2	2	0.42
Few <sup>a</sup>	4	7	
Many	9	3	0.1
Confluent sheets	4	1	0.3
Megalocytic IN	4	0	0.003
Tubulocentric	11	3	0.013
Intratubular	6	1	0.088
Necrosis	5	1	0.2
Giant cells	7	5	1
Glomerular granulomas	1	0	–
Microorganisms	8	0	0.006
Crystals	0	0	–
Other inflammatory cells			
Eosinophils	4	8	0.036
Neutrophils	7	10	0.019
Plasma cells	5	5	0.69
Banff scores (mean)			
i	1.6	1.6	1
t	1.9	1.5	0.38
i2t2 or more	6	4	1
g	0.15	0.3	0.6
ptc	0.08	0.1	0.95
v	0.6	0.7	0.53
v1 or more	2	3	0.62
ci	1.3	1.3	0.9
ct	1.15	1.2	0.9
cv	0.6	0.7	0.5
ah	0.5	0.3	0.85
PTC C4d	0/8	1/7	–
Other findings			
Thrombotic microangiopathy	3	0	–
Immune complex GN	0	1	–

GN, glomerulonephritis; IN, interstitial nephritis; PTC, peritubular capillary.

<sup>a</sup>few = three or fewer

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

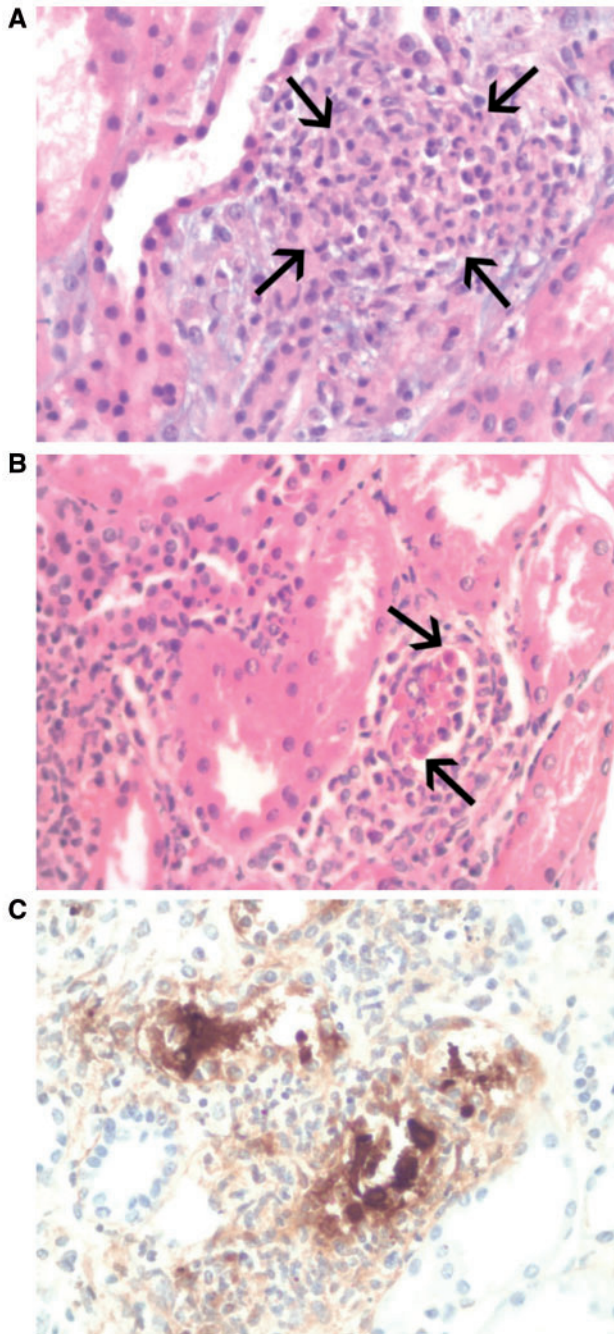


Fig. 2. Adenovirus tubulointerstitial nephritis presented with (A) granulomatous inflammation comprised of macrophages and neutrophils between tubules (arrows, H&E, 400 $\times$ ), (B) viral cytopathic changes manifesting as occasional appreciable nuclear smudging (arrows, H&E, 400 $\times$ ) and (C) positive adenovirus immunohistochemistry (400 $\times$ ).

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

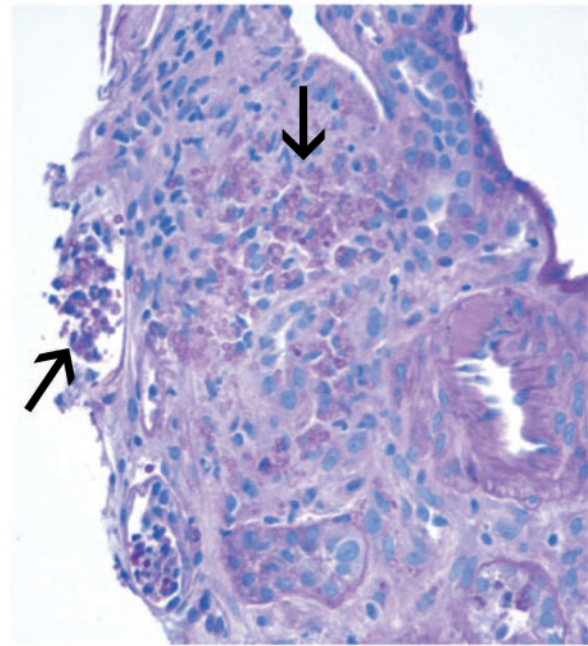


Fig. 3. A PAS stain shows yeast-like fungal organisms in interstitial granulomas and in tubules (arrows) in a case of GIN due to *C. albicans* (PAS, 400 $\times$ ).

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, megalocytic 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

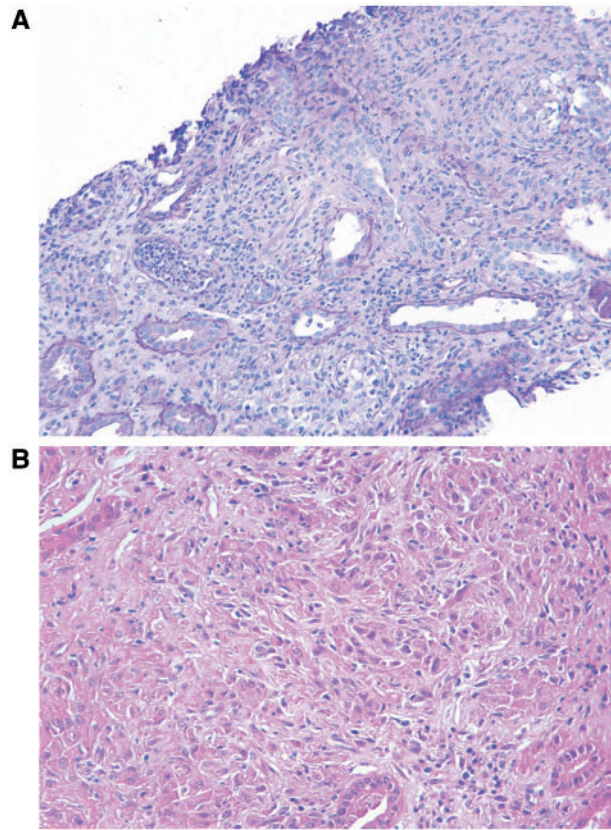


Fig. 4. (A) MIN with sheets of epithelioid macrophages, tubular destruction and acute epithelial injury with necrotic casts (PAS, 200 $\times$ ). (B) MIN due to *E. coli* infection showing confluent nodular clusters of macrophages with granular cytoplasm. The background is edematous with a slight lymphoid infiltrate (H&E, 200 $\times$ ).

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. Concurrence 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

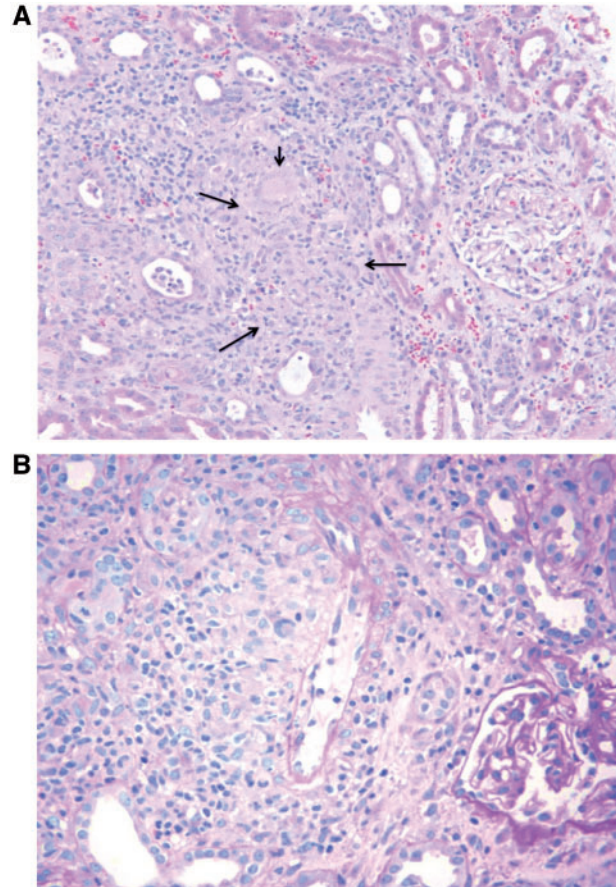


Fig. 5. (A) A poorly formed interstitial granuloma with giant cells is highlighted by arrows (H&E, 100 $\times$ ). (B) Deeper sections revealed granulomatous arteritis in a patient with recurrent granulomatosis with polyangiitis on posttransplant day 11. There were no glomerular crescents (PAS, 200 $\times$ ).

Table 4. Outcome

Treatment response	Infectious	Noninfectious	P
Complete response (n = 6)	1	5	
Partial response (n = 8)	7	1	
Graft loss (n = 4)	4	0	0.006
No data (n = 4)			

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.

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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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## References

- Petersen HJ, Smith AM. The role of the innate immune system in granulomatous disorders. *Front Immunol* 2013; 4: 120
- Chensue SW. Chemokines in innate and adaptive granuloma formation. *Front Immunol* 2013; 4: 43
- Jennette JC, Thomas DB. Pauci-immune and antineutrophil cytoplasmic autoantibody-mediated crescentic glomerulonephritis and vasculitis. In: Jennette JC, Olson JL, Silva FG, et al (eds). *Heptinstall's Pathology of the Kidney*. Philadelphia, PA: Wolters Kluwer, 2015, 685–713.
- Mignon F, Mery JP, Mougenot B, et al. Granulomatous interstitial nephritis. *Adv Nephrol Necker Hosp* 1984; 13: 219–245
- Viero RM, Cavallo T. Granulomatous interstitial nephritis. *Hum Pathol* 1995; 26: 1347–1353
- Meehan SM, Josephson MA, Haas M. Granulomatous tubulointerstitial nephritis in the renal allograft. *Am J Kidney Dis* 2000; 36: E27
- Hotta K, Fukasawa Y, Sasaki H, et al. Granulomatous tubulointerstitial nephritis in a renal allograft: three cases report and review of literature. *Clin Transplant* 2012; 26 Suppl 24: 70–75
- Napathorn S, Praditpornsilpa K, Yenrudi S. Granulomatous interstitial nephritis in renal transplant recipient. *J Med Assoc Thai* 1996; 79: 44–48
- Gupta P, Rana DS, Bhalla AK, et al. Renal failure due to granulomatous interstitial nephritis in native and allograft renal biopsies: experience from a tertiary care hospital. *Ren Fail* 2014; 36: 1468–1470
- Kirk AD, Hale DA, Mannon RB, et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). *Transplantation* 2003; 76: 120–129
- Sis B, Grynoch R, Murray AG, et al. Antibody-mediated rejection with a striking interstitial monocyte/macrophage infiltration in a renal allograft under FTY720 treatment. *Am J Kidney Dis* 2008; 51: 127–130
- Bagnasco SM, Gottipati S, Kraus E, et al. Sarcoidosis in native and transplanted kidneys: incidence, pathologic findings, and clinical course. *PLoS One* 2014; 9: e110778
- Higgins RM, Cahn AP, Porter D, et al. Mycobacterial infections after renal transplantation. *QJ Med* 1991; 78: 145–153
- Goncalves AR, Caetano MA, Paula FJ, et al. Tuberculous interstitial granulomatous nephritis in renal transplants: report of three cases. *Transplant Proc* 1992; 24: 1911
- al-Sulaiman MH, Dhar JM, al-Hasani MK, et al. Tuberculous interstitial nephritis after kidney transplantation. *Transplantation* 1990; 50: 162–164
- Lichtenstein IH, MacGregor RR. Mycobacterial infections in renal transplant recipients: report of five cases and review of the literature. *Rev Infect Dis* 1983; 5: 216–226
- Jefferson HJ, Ho TB. Tuberculosis after renal transplantation. *Nephrol Dial Transplant* 1999; 14: 1341–1342
- Kaslikova J, Tousek J, Jirka J, et al. Miliary tuberculosis in a patient after renal transplantation. *Czech Med* 1978; 1: 116–121
- Ozdemir BH, Sar A, Uyar P, et al. Posttransplant tubulointerstitial nephritis: clinicopathological correlation. *Transplant Proc* 2006; 38: 466–469
- Yang CW, Lee SH, Choi YJ, et al. Chronic granulomatous interstitial nephritis: unusual complication of acute pyelonephritis. *Nephron* 1996; 72: 305–307
- Tse KC, Chan TM, Wong SS, et al. Granulomatous interstitial nephritis of the allograft kidney associated with rhodococcal pulmonary infection. *Nephrol Dial Transplant* 2004; 19: 486–490
- Asim M, Chong-Lopez A, Nickeleit V. Adenovirus infection of a renal allograft. *Am J Kidney Dis* 2003; 41: 696–701
- Alsaad KO, Tobar A, Belanger E, et al. Late-onset acute hemorrhagic necrotizing granulomatous adenovirus tubulointerstitial nephritis in a renal allograft. *Nephrol Dial Transplant* 2007; 22: 1257–1260
- Lachiewicz AM, Cianciolo R, Miller MB, et al. Adenovirus causing fever, upper respiratory infection, and allograft nephritis complicated by persistent asymptomatic viremia. *Transpl Infect Dis* 2014; 16: 648–652
- Parasuraman R, Zhang PL, Samarapungavan D, et al. Severe necrotizing adenovirus tubulointerstitial nephritis in a kidney transplant recipient. *Case Rep Transplant* 2013; 2013: 969186
- Storsley L, Gibson IW. Adenovirus interstitial nephritis and rejection in an allograft. *J Am Soc Nephrol* 2011; 22: 1423–1427
- Peya CV. Fungal infections in solid-organ transplantation. *Clin Infect Dis* 1993; 16: 677–688
- Shen SY, Hall-Craggs M, Posner JN, et al. Recurrent sarcoid granulomatous nephritis and reactive tuberculin skin test in a renal transplant recipient. *Am J Med* 1986; 80: 699–702
- Lien YH, Hansen R, Kern WF, et al. Ciprofloxacin-induced granulomatous interstitial nephritis and localized elastolysis. *Am J Kidney Dis* 1993; 22: 598–602
- Brown JH, Jos V, Newstead CG, et al. Sarcoid-like granulomata in a renal transplant. *Nephrol Dial Transplant* 1992; 7: 173
- Kukura S, Viklicky O, Lacha J, et al. Recurrence of sarcoidosis in renal allograft during pregnancy. *Nephrol Dial Transplant* 2004; 19: 1640–1642
- Vargas F, Gedalia A, Craver RD, et al. Recurrence of granulomatous interstitial nephritis in transplanted kidney. *Pediatr Transplant* 2010; 14: e54–e57
- Aouizerate J, Matignon M, Kamar N, et al. Renal transplantation in patients with sarcoidosis: a French multicenter study. *Clin J Am Soc Nephrol* 2010; 5: 2101–2108
- Hobbs DJ, Barletta GM, Chung JY, et al. Isolated sarcoid granulomatous interstitial nephritis in pediatrics: a case report and review of literature. *Clin Nephrol* 2009; 72: 410–413
- Onyekpe I, Shenoy M, Denley H, et al. Recurrent tubulointerstitial nephritis and uveitis syndrome in a renal transplant recipient. *Nephrol Dial Transplant* 2011; 26: 3060–3062



36. Khaira A, Bagchi S, Sharma A, et al. Renal allograft tuberculosis: report of three cases and review of literature. *Clinical and experimental nephrology* 2009; 13: 392–396
37. Yamamoto I, Yamaguchi Y, Horita S, et al. Granulomatous tubulointerstitial nephritis in early renal allograft: a case report. *Clin Transplant* 2007; 21: 23–26
38. Nunota N, Honda H, Shibata T, et al. Granulomatous interstitial nephritis in a renal allograft. *CEN Case Rep* 2012; 1: 12–15
39. Wasi N, Reddivari V, Salinas-Madriral L, et al. A rare case of acute renal failure due to massive renal allograft infiltration with *Candida glabrata*. *Nephrol Dial Transplant* 2008; 23: 374–376
40. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of C4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant* 2014; 14: 272–283
41. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998; 316: 1236–1238
42. Bijol V, Mendez GP, Nose V, et al. Granulomatous interstitial nephritis: a clinicopathologic study of 46 cases from a single institution. *Int J Surg Pathol* 2006; 14: 57–63
43. Lapasia JB, Kambham N, Busque S, et al. Renal allograft granulomas in the early post-transplant period. *NDT Plus* 2010; 3: 397–401
44. Baden LR, Digumarthy SR, Guimaraes AS, et al. Case records of the Massachusetts General Hospital. Case 35-2009. A 60-year-old male renal-transplant recipient with renal insufficiency, diabetic ketoacidosis, and mental-status changes. *N Engl J Med* 2009; 361: 1980–1989
45. Koike J, Yamaguchi Y, Horita S, et al. A case of renal transplantation with granulomatous nephritis and arteritis associated with *Pseudomonas aeruginosa* infection. *Clin Transplant* 2007; 21: 27–30
46. Mahmood A, Poller DN, Ramage JK. Are renal microgranulomas related to inflammatory tubular destruction? *J Clin Pathol* 2004; 57: 551–552
47. Josephson MA, Chiu MY, Woodle ES, et al. Drug-induced acute interstitial nephritis in renal allografts: histopathologic features and clinical course in six patients. *Am J Kidney Dis* 1999; 34: 540–548
48. Magil AB. Drug-induced acute interstitial nephritis with granulomas. *Hum Pathol* 1983; 14: 36–41
49. Joss N, Morris S, Young B, Geddes C. Granulomatous interstitial nephritis. *Clin J Am Soc Nephrol* 2007; 2: 222–230
50. Nিকেleit V, Mengel M, Colvin RB. Renal Transplant Pathology. In: Jennette JC, Olson JL, Silva FG, et al (eds). *Heptinstall's Pathology of the Kidney*. Wolters Kluwer, Philadelphia, PA: Wolters Kluwer, 2015, 1321–1459
51. Biggar WD, Crawford L, Cardella C, et al. Malakoplakia and immunosuppressive therapy. Reversal of clinical and leukocyte abnormalities after withdrawal of prednisone and azathioprine. *Am J Pathol* 1985; 119: 5–11
52. McGregor SM, Chon WJ, Kim L, et al. Clinical and pathological features of kidney transplant patients with concurrent polyomavirus nephropathy and rejection-associated endarteritis. *World J Transplant* 2015; 5: 292–299
53. Schwarz A, Krause PH, Kunzendorf U, et al. The outcome of acute interstitial nephritis: risk factors for the transition from acute to chronic interstitial nephritis. *Clin Nephrol* 2000; 54: 179–190