



CKJ REVIEW

Granulomatous interstitial nephritis

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Abstract

Granulomatous interstitial nephritis (GIN) is a rare entity detected in ~0.5–0.9% of all renal biopsies. GIN has been linked to several antibiotics such as cephalosporins, vancomycin, nitrofurantoin and ciprofloxacin. It is also associated with NSAIDs and granulomatous disorders such as sarcoidosis, tuberculosis, fungal infections, and granulomatosis with polyangiitis. Renal biopsy is critical in establishing this diagnosis, and the extent of tubular atrophy and interstitial fibrosis may aid in determining prognosis. Retrospective data and clinical experience suggest that removal of the offending agent in conjunction with corticosteroid therapy often results in improvement in renal function. We describe a patient with a history of multiple spinal surgeries complicated by wound infection who presented with confusion and rash with subsequent development of acute kidney injury. Urinalysis demonstrated pyuria and eosinophiluria, and renal biopsy revealed acute interstitial nephritis with granulomas. These findings were attributed to doxycycline treatment of his wound infection. This review explores the clinical associations, presentation, diagnosis, and treatment of this uncommon cause of acute kidney injury.

Key words: AIN, AKI, doxycycline, granuloma

Background

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury where antibiotics are the most common offending agents [1, 2]. The presence of granulomas with AIN is rare and antibiotics such as vancomycin, ciprofloxacin, nitrofurantoin, penicillin and cephalosporins have been implicated [3–5]. To our knowledge, doxycycline-induced granulomatous interstitial nephritis (GIN) has not been previously described.

Case report

A 69-year-old Caucasian man with a history of untreated hepatitis C, type 2 diabetes mellitus, chronic obstructive pulmonary disease, depression and chronic back pain for which he underwent four cervical and four lumbar spine surgeries presented with confusion, diffuse rash and leucocytosis from his rehabilitation facility. Two months prior to admission, after his last posterior spinal fusion, he developed a wound infection with coagulase

negative *Staphylococcus* species. He was treated with intravenous vancomycin for 1 month. Sixteen days prior to admission, he was switched from vancomycin to doxycycline 100 mg by mouth twice daily. Ten days prior to admission, the patient developed a pruritic, erythematous rash involving his face, arms, torso and back. Doxycycline was discontinued, and he was started on prednisone 40 mg daily for 4 days. His rash did not improve; he became delirious and was transferred for further evaluation.

His medications included amitriptyline, pregabalin, methadone, fluoxetine, trazodone, loratadine, ranitidine, docusate senna, polyethylene glycol, bisacodyl suspension, hydrocortisone/aloe topical cream and menthol/camphor topical lotion. He was not taking non-steroidal anti-inflammatory medications. He had no known allergies.

On physical exam, the patient was afebrile, normotensive and not hypoxic. He had a diffuse erythematous maculopapular rash on his face, arm, chest, abdomen and back with excoriations on his face and arms. He had a grossly normal ocular, oral, heart, lung and neurologic exam.

Received: March 4, 2015. Accepted: June 10, 2015

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Laboratory results on admission were significant for creatinine of 0.8 mg/dL and white blood cell count of 16.89k/mm³ of which 53% were eosinophils (Table 1). Non-contrast CT imaging of the thoracolumbar spine, chest, abdomen and pelvis showed non-specific perinephric stranding and bladder wall thickening without evidence of obstruction and mild splenomegaly. There was no clear evidence of infection or abscess.

He was empirically treated with vancomycin, piperacillin-tazobactam and briefly ciprofloxacin for a urinary tract infection. Cultures were negative, and the antibiotics were discontinued. However, the rash and altered mental status persisted. A skin biopsy was performed and was non-diagnostic.

By Day 5 of his hospitalization, his creatinine had risen to 1.9 mg/dL with a concomitant increase in AST and ALT levels. Urinalysis revealed 1+ proteinuria, 16 RBC/hpf and 7 WBC/hpf with eosinophiluria.

A kidney biopsy was performed. Light microscopy demonstrated relatively uninvolved glomeruli and marked diffuse interstitial inflammation composed of activated lymphocytes, plasma cells and numerous eosinophils (>50/hpf) with frequent foreign body giant cells associated with non-caseating granulomas (Figures 1 and 2). There was moderate acute tubular injury and presumed mild interstitial fibrosis. Special stains for acid-fast bacilli, bacteria (Brown & Hopps) and fungi (GMS) were negative. Immunofluorescence revealed non-specific findings. Electron microscopy showed scattered immune deposits possibly corresponding to IgM on immunofluorescence, suggesting an immune-mediated process; however, the extensive granulomatous inflammation was considered the prevailing pathologic process. He was diagnosed with severe AIN with numerous

eosinophils and foreign body giant cell granulomas, secondary to doxycycline.

He underwent another skin biopsy that demonstrated spongiotic and interface dermatitis with eosinophils compatible with drug reaction with eosinophilia and systemic symptoms (DRESS). He was started on prednisone 60 mg by mouth daily. Two days later, his creatinine peaked at 3.1 mg/dL, but declined to 1.7–1.9 mg/dL while on prednisone.

On Day 17 of his hospitalization, the patient was transferred to the medical intensive care unit for worsening altered mental status and intermittent apneic episodes. His course was further complicated by Stevens Johnson syndrome/toxic epidermal necrolysis. Ciprofloxacin, which was started empirically a few days prior, was the presumed culprit. A few days later, the patient developed respiratory failure and hypotension necessitating mechanical ventilatory support and vasopressors. Blood cultures grew methicillin-sensitive *Staphylococcus aureus*. He ultimately succumbed to refractory septic shock and multi-organ failure.

Discussion

This patient's exposure to doxycycline was followed by rash, eosinophilia, eosinophiluria and acute kidney injury resulting in a biopsy-proven diagnosis of GIN. Although the patient was exposed to vancomycin, piperacillin-tazobactam and ciprofloxacin prior to renal biopsy, the patient's rash and laboratory derangements were traced to the initiation of doxycycline. Renal manifestations of AIN typically occur within 3 weeks of starting the offending drug in ~80% of cases, where the average delay is ~10 days with antibiotics [5]. The patient's exposure to

Table 1. Laboratory data during hospitalization at Johns Hopkins Hospital

Variable	Hospital Day 1	Hospital Day 7 (Day 1 prednisone, after biopsy on Day 6)	Hospital Day 8 (peak creatinine)	Hospital Day 21 (partial remission – new baseline)	Reference range
Sodium	133	134	134	132	135–148 mEq/L
Potassium	4.5	4.3	5.2	4.5	3.5–5.1 mEq/L
Chloride	100	101	102	97	96–109 mEq/L
Carbon dioxide	22	19	18	22	21–31 mEq/L
Blood urea nitrogen ^a	15	34	47	39	7–22 mg/dL
Creatinine ^a	0.8	2.6	3.1	1.7	0.6–1.3 mg/dL
Glucose ^a	86	134	251	359	60–99 mg/dL
White blood cells	16.89	14.99	13.64	9.18	4.5–11k/mm ³
Eosinophils (%)	53	22	7	1	<1–4
Polymorphonuclear cells (%)	42	63	86	84	31–46
Lymphocytes (%)	3	7	2	12	24–44
Monocytes (%)	1	4	2	2	2–11
Hemoglobin	15.7	13.7	13.1	13.2	13.9–16.3 g/dL
Mean corpuscular volume	84.1	83.9	84.2	85.1	80–100 fL
Platelet	21 ^b	174	160	117	150–300k/mm ³
INR	1.6	Not measured	Not measured	1.2	0.9–1.1
Albumin	2.7	2.3	2.6	2.5	3.5–5.3 g/dL
Total protein	6.3	6.1	6.2	6.3	6.0–8.2 g/dL
Total bilirubin	0.7	0.7	0.8	0.8	0–1.2 mg/dL
Alkaline phosphatase	98	89	92	85	30–120 U/L
Aspartate amino transferase	Hemolyzed, repeat was 40	81	75	35	0–37 U/L
Alanine amino transferase	33	101	100	50	0–40 U/L
C-reactive protein	1.0	Not measured	Not measured		<0.5 mg/dL

^aConversion factor for units: Serum creatinine in mg/dL to μ mol/L, $\times 88.4$; blood urea nitrogen in mg/dL to mmol/L, $\times 0.357$; glucose mg/dL to mmol/L, 0.05551 .

^bPlatelet count may not have been accurate. Although no clot was documented to have been found in the tube, repeat platelet count 6 h later was 129 k/cc³.

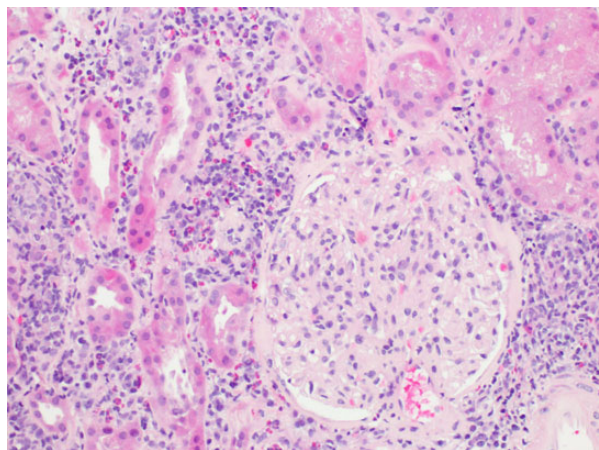


Fig. 1. Hematoxylin and eosin stain at $\times 200$ magnification on light microscopy showing an uninvolved glomerulus in a background of interstitial inflammation with numerous eosinophils.

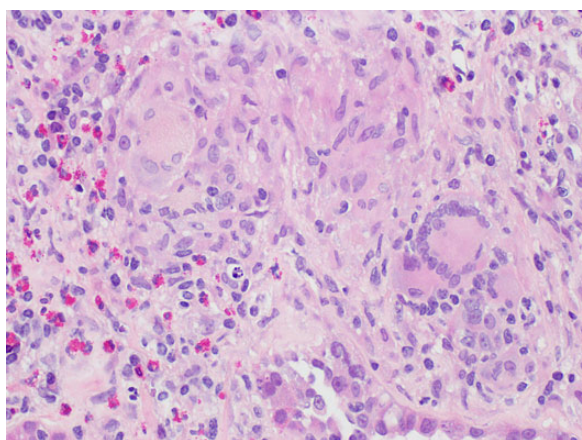


Fig. 2. Hematoxylin and eosin stain at $\times 400$ magnification on light microscopy demonstrating a poorly formed granuloma with foreign body-type giant cells.

vancomycin preceded this presentation by months, and generally vancomycin-induced interstitial nephritis appears 7–25 days after drug onset; therefore, it is less likely this drug was responsible [6]. Piperacillin-tazobactam and ciprofloxacin were initiated only a few days prior to the patient's rise in creatinine and urine abnormalities, which would ordinarily be too short to develop interstitial nephritis with granulomas. The patient's concomitant rash and eosinophilia following treatment with doxycycline also suggest this was the most likely offending agent.

Incidentally, serum quantiferon testing for tuberculosis was positive 13 days following renal biopsy. Although special staining for acid-fast bacilli on renal biopsy tissue was negative, this does not exclude tuberculosis-induced GIN. However, other signs of active tuberculosis were lacking. Latent tuberculosis was a possibility, but treatment was deferred in light of active Stevens Johnson syndrome.

The patient also had a history of untreated hepatitis C, which can be associated with renal complications such as cryoglobulinemic glomerulonephritis, membranoproliferative glomerulonephritis, membranous nephropathy, IgA nephropathy, polyarteritis nodosa, fibrillary and immunotactoid glomerulonephritis and interstitial nephritis [7, 8]. In a retrospective report of 68 patients

with hepatitis C and renal dysfunction who underwent renal biopsy, 2 had interstitial nephritis, and 1 had GIN attributed to sarcoidosis [9]. A direct association between hepatitis C and GIN has not been established.

The role of renal biopsy was critical in excluding a progressive glomerulonephritis and in delineating the extent of inflammation, fibrosis and eosinophilic infiltration. The findings of mild tubulointerstitial fibrosis are associated with a more favorable response to corticosteroid therapy [10]. Unfortunately, despite a partial recovery in renal function, he ultimately expired from septic shock and multi-system organ failure due to Stevens Johnson syndrome/toxic epidermal necrolysis.

Epidemiology and clinical associations

GIN occurs in 0.5–0.9% of native kidney biopsies [11–16]. The relative contribution of different etiologies to GIN is unknown since our knowledge is based on case series and case reports for the description of this condition. In a report by Mignon et al. [12] of 32 cases, ~28% were due to drugs, 16% were caused by granulomatosis with polyangiitis (GPA) and 9% were attributed to sarcoidosis and tuberculosis. In the series presented by Viero and Cavallo [15], 25% of cases were due to drugs, sarcoidosis and infections each. Bijol et al. [13] reviewed 9779 biopsies between January 1987 and July 2004 to describe cases of GIN, where a single but definite granuloma was deemed enough for inclusion. They found 46 cases of which 38 had available clinical information. Seventeen patients had drug-induced GIN, 11 patients had sarcoidosis-related GIN and 2 had GPA. Javaud et al. [17] evaluated 40 consecutive renal biopsies between January 1991 and February 2004 with GIN defined as the presence of at least one epithelioid granuloma in the interstitium. The majority of their cases were linked to sarcoidosis (50%), where medications (17.5%) and tuberculosis (7.5%) accounted for fewer cases [17]. The variability in these series can be explained by both sampling and publication bias of these cohorts. Known causes of GIN are listed in Table 2.

Common causes of GIN

Sarcoidosis

Renal involvement in sarcoidosis is most often due to nephrocalcinosis, hypercalciuria or calculi secondary to hypercalcemia resulting from increased 1,25 dihydroxyvitamin D₃ production by activated macrophages in areas of inflammation [26–28]. Granulomatous renal involvement is considered rare and is mostly described in case reports or case series [26]. However, ~7–27% of patients with sarcoidosis have evidence of granulomatous tubulointerstitial nephritis on post-mortem series, although this may not result in clinically significant renal disease [29, 30].

Most patients with GIN in sarcoidosis present with extrarenal manifestations such as pulmonary, skin or eye involvement [14, 27, 31–33]. However, there are a few series reporting sarcoid GIN without extrarenal involvement [32, 34]. In addition, there are several cases where the diagnosis of GIN then leads to a subsequent diagnosis of sarcoidosis [14, 28, 35]. It is therefore possible that some cases of idiopathic GIN may represent unrecognized renal limited sarcoidosis [32]. Thus, patients with sarcoidosis can develop GIN at any time during the course of their disease, and it may even precede the diagnosis in some cases [17].

Membranous nephropathy can be detected in conjunction with GIN in patients with sarcoidosis. Three case reports document patients with nephrotic syndrome and sarcoidosis who undergo renal biopsy and are found to have both pathologic

Table 2. Causes and associated features of granulomatous interstitial nephritis [3, 13–25]

	Antimicrobials	Analgesics	Other drugs	Infections	Inflammatory /Rheumatologic
Etiology	Penicillin Methicillin Ampicillin Amoxicillin Oxacillin Cephalothin Erythromycin Spiramycin Rifampicin Vancomycin Sulfonamides Ciprofloxacin Levofloxacin Gentamicin Nitrofurantoin Acyclovir Clotrimazole Doxycycline	Fenoprofen Ketoprofen Indomethacin Diclofenac Clometacine Ibuprofen Diflunisal Benoxaprofen Paracetamol Dihydrocodeine Naprosyn	Allopurinol Omeprazole Alendronate Furosemide Hydrochlorothiazide Chlorothiazide Triamterene Amiloride Chlorpropamide Tienlinic acid Captopril Carbamazepine Lamotrigine Levetiracetam Phenytoin Phenindione Sulfasalazine	<i>Mycobacterium tuberculosis</i> <i>Mycobacterium leprae</i> <i>Mycobacterium kansasii</i> Histoplasmosis Candidiasis Toxoplasmosis <i>Tricosporon laibachii</i> <i>Cryptococcus neoformans</i> <i>Escherichia coli</i> Epstein-Barr virus	Sarcoidosis TINU syndrome Intestinal bypass Heroin Oxalosis Crohn's disease Granulomatosis with polyangiitis (GPA) Eosinophilic granulomatosis with polyangiitis (EGPA) Bacillus Calmette-Guerin therapy
Epidemiology	Usually presents few weeks after exposure Often middle-aged patients	Usually months after exposure Often middle-aged patients	Diuretics reported onset >4 weeks after exposure Often middle-aged patients	TB more common in those with Indian or African descent Consider fungal and mycobacterial causes post-transplant TB patients are younger	TINU in adolescent girls Sarcoidosis often in African Americans GPA and EGPA have bimodal age distribution
Presentation	May have hypersensitivity symptoms, variable degree of renal failure, mild proteinuria, ±microscopic hematuria and pyuria	Can present with nephrotic syndrome	May also have hypersensitivity symptoms, varying degrees of renal failure, may necessitate renal replacement therapy	Insidious presentation, diagnosis often is delayed, can have extrarenal symptoms corresponding to infectious etiology	Depends on underlying cause Diagnosis of sarcoidosis can occur at any time relative to renal involvement Uveitis often follows renal failure in TINU
Histology	Ill-defined, non-caseating granulomas	Ill-defined, non-caseating granulomas	Ill-defined, non-caseating granulomas	Necrotizing granulomas	Necrotizing, well-formed granulomas in GPA, EGPA Non-caseating, well-formed granulomas in sarcoidosis, TINU, Crohn's disease

lesions [28, 36, 37]. These patients responded well to glucocorticoid therapy.

Drugs

Antibiotics

Antibiotics are a well-established etiology of GIN, and the number of implicated agents has grown over time. Sulfonamide therapy was described by More et al. [38] in 1946 to cause granulomatous renal lesions in 8/22 autopsies reviewed. Typically, granulomas exhibited more widespread interstitial infiltration and involved the cortex more than the medulla in these cases. Penicillins (ampicillin, oxacillin and methicillin) and cephalosporins have been linked to GIN in several case reports [12, 17, 39–42]. Fluoroquinolones, which have been associated with AIN, ATN and crystalluria, have also been described to cause GIN. Ramalakshmi et al. [43] reported levofloxacin-induced GIN in a patient treated for a urinary tract infection who subsequently developed fever,

rise in liver enzymes and acute kidney injury. Ciprofloxacin has also been reported in association with GIN, where a patient was treated for cellulitis [4]. Nitrofurantoin has been reported as the cause of GIN in two cases, and in both cases, patients improved with drug withdrawal [3, 18]. Vancomycin was added to this list of offenders in 2007 when a patient developed DRESS syndrome and GIN, similar to our case presentation with doxycycline [6]. Of note, the latency period between antibiotic use and the diagnosis of GIN is shorter than that seen with other medications.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to cause GIN in several case reports and notably in at least three large case series. Schwarz et al. [44] described two patients who presented with renal insufficiency of whom, one developed end-stage renal disease after months of treatment with NSAIDs (ketoprofen/indomethacin and diclofenac/indomethacin). Viero and Cavallo [15] found two instances of

GIN out of 12 where naprosyn and aspirin were implicated. Javaud et al. [17] found 7 out of 40 consecutive renal biopsies between January 1991 and February 2004 to have GIN that were considered drug induced. Two of these patients were exposed to ibuprofen and tenoxicam. Finally, Joss et al. [14] described two patients between 1990 and 2004 who were found to have GIN after exposure to omeprazole/diclofenac and sulfasalazine/indomethacin, respectively. Both patients presented with eGFR of ~17 mL/min but increased to ~56 mL/min after prednisone treatment.

NSAID-induced AIN with or without granulomas often occur after months of exposure, with the mean duration of 6 months [5]. Although proteinuria is usually subnephrotic in patients with GIN, patients with NSAID-related disease can develop nephrotic syndrome [5].

Diuretics

Some of the earliest reports of diuretic-induced GIN were in 1983. Ebert described a patient treated with hydrochlorothiazide and triamterene who developed fevers, flank pain, eosinophilia, pyuria and acute kidney injury [45]. Magil et al. reported nine patients with drug-induced GIN between 1977 and 1981 [46]. These patients were treated with hydrochlorothiazide, triamterene, fenoprofen and/or furosemide. None of these patients had pre-existing renal disease, tuberculosis or sarcoidosis. Renal failure typically occurred 4–10 weeks after introduction of the drug, which is longer than reported with antibiotics. Amiloride and hydrochlorothiazide were implicated in a later case report in 1995 [19]. These patients improved with drug withdrawal.

Other medications

Allopurinol and anti-epileptics have been associated with GIN. Allopurinol is also associated with granulomatous hepatitis. In the first description of allopurinol-induced GIN, the patient improved with drug withdrawal and prednisone therapy [47]. GIN has also been traced to carbamazepine, phenytoin and levetiracetam [16, 48, 49].

Infection

Tuberculosis is the most common infectious etiology of GIN [50]. Most cases are reported in patients of Asian Indian or African descent, which may reflect the higher incidence of disease in these populations [16, 50–53]. Renal involvement is insidious and can remain undetected for up to 20 years [54]. The disease is easily overlooked, such that diagnoses are made during an operation or post-mortem [55]. The first description of GIN as a sole manifestation of renal tuberculosis was made by Mallinson et al. [53] in 1981. They describe three patients with pulmonary tuberculosis and advanced renal disease secondary to chronic tubulointerstitial nephritis with granulomas. One patient developed end-stage renal disease despite treatment, and the other two patients had progressive decline in renal function with treatment, which was attributed to drug toxicity.

A case series from India assessed 2798 renal biopsies performed between January 2000 and October 2012 and found that 14 patients were diagnosed with GIN during that period [16]. Tuberculosis was considered the culprit in 9 out of the 14 cases. Mean age in this cohort was 35 years, which is younger than what is usually seen in patients with GIN. Pulmonary involvement and/or mediastinal lymphadenopathy was evident in four cases. Mean serum concentration at presentation was 6.7 mg/dL and six patients required dialysis initially, which reflects the delay in diagnosing this condition. Two patients

were able to discontinue dialysis with treatment, but the majority of patients ultimately progressed to CKD or ESRD.

Fungal and atypical bacterial infections have also been implicated in GIN. Disseminated *Mycobacterium kansasii* infection has been reported in association with GIN and liver granulomas [20]. Ogura et al. [21] reported two cases of fungal GIN related to *Trichosporon laibachii* in one patient treated with chemotherapy for pharyngeal cancer and the second related to *Candida albicans* in a patient treated with steroids for asthma. Another report describes a patient with untreated systemic lupus erythematosus with CD4 lymphopenia who developed cryptococcal GIN [22]. These cases highlight the consideration of fungal interstitial nephritis in immunocompromised patients.

Although unusual, immunocompetent patients can also develop fungal GIN as reported by Nasr et al. [56]. In this case, a male patient was found to have dialysis-dependent acute kidney injury, his renal biopsy revealed GIN and he was diagnosed with disseminated *Histoplasma capsulatum* after careful inspection of renal biopsy tissue for yeast forms and serum antigen measurement.

Others

Tubulointerstitial nephritis with uveitis (TINU) can also cause GIN. This rare condition, which generally affects adolescent girls, has no clear underlying cause but has been linked with rheumatoid arthritis, infections, NSAID administration, antibiotics and Chinese herbs [57–62]. Patients may be misdiagnosed as having drug-induced interstitial nephritis, because uveitis often occurs after the onset of kidney disease [57]. In Joss et al., two patients were diagnosed with TINU out of 18 cases of GIN [14]. One patient presented with simultaneous renal failure and uveitis and the other developed uveitis following a diagnosis of idiopathic GIN. Granulomatous TINU has also been associated with a salt wasting nephropathy [63]. Treatment with corticosteroids generally leads to an improvement in creatinine clearance [13, 14, 57, 59, 63].

GIN can be a histologic finding in patients with GPA. Although Bijol et al. cites the frequency of GIN in GPA between 5 and 67% depending on the series, our review of the literature demonstrates a frequency on the order of 5–16% [12, 13, 15–17]. Patients often present with pulmonary symptoms, renal failure, microscopic hematuria and moderate but usually subnephrotic range proteinuria.

Post-renal transplant GIN has also been described. The reported incidence of GIN in renal allografts is similar to that of native kidneys: 0.6–1% [23–25]. Although acute rejection is a common cause of interstitial nephritis, it is not associated with granuloma formation [23]. Rather, infections such as *Mycobacterium tuberculosis*, *C. albicans*, *Escherichia coli* and viruses are more commonly responsible [23–25, 64, 65]. This reflects an increased predisposition to GIN secondary to increased infection risk from immunosuppression for allograft maintenance.

Crohn's disease, oxalosis and intravesicular bacillus Calmette–Guerin have also been responsible for causing GIN in a few cases [13, 15, 17]. The etiology for GIN remains obscure in ~10% of cases [13, 17].

Pathophysiology of medication-induced GIN

The putative mechanisms by which medications induce AIN have been described using experimental models and through renal biopsy findings. Drug-induced AIN is most likely related to immune reactions as few patients exposed to a particular

drug develop AIN. The response is not dose dependent, and it can be associated with extrarenal signs of hypersensitivity [5]. Furthermore, AIN can recur when patients are re-introduced to the inciting agent or a very similar agent. In experimental models, AIN can occur due to an immune response against an antigen that originates within the kidney or an extrarenal antigen that is deposited in the kidney [66–68]. Potentially, a drug can bind to part of the tubular basement membrane and act as a hapten. Alternatively, the drug can mimic an antigen in the tubular basement membrane or intersitium where via molecular mimicry an immune response targets both the drug and the similar antigen [5]. The response is most likely cell mediated in nature given the number of lymphocytes and macrophages seen on light microscopy specimens and the paucity of immune deposits seen on immunofluorescence. GIN has been attributed to a delayed type hypersensitivity reaction and cell-mediated response type 1 helper T cells [5].

Clinical manifestations and histologic findings

Clinical manifestations, laboratory signs and histologic findings vary in patients with GIN depending on the underlying cause. Generally, there is no predilection for either gender [13–15, 17]. GIN can manifest at any age; however, the mean and median ages of presentation in most series were in the fifth and sixth decade of life [13–15, 17]. Patients with tuberculosis-induced GIN tend to be younger [16]. GIN can result in varying degrees of renal insufficiency and necessitate the initiation of dialysis. The mean creatinine in two series was 4.1–5.1 mg/dL, and the median creatinine clearance in three series ranged between 21 and 27 mL/min [13–15, 17, 28]. Approximately one-third of patients with drug-induced GIN in one series had signs of hypersensitivity such as arthralgia, fevers and eosinophilia [17]. Patients with NSAID-induced GIN often have higher levels of proteinuria (nephrotic range at times) and less eosinophilia [5, 10]. Otherwise, patients usually demonstrate mild proteinuria, normal blood pressures and less frequently have sterile pyuria or microscopic hematuria [12, 13, 17].

On renal biopsy, granulomas with non-necrotizing features are associated with drug-induced GIN and sarcoidosis, whereas, necrotizing granulomas are common in patients with GPA, fungal or tuberculosis-induced GIN [13, 17]. Drug-induced GIN leads to more loose appearing aggregates of epithelioid macrophages, but granulomas in sarcoidosis tend to be rather well defined [13, 45]. Although these findings are suggestive of certain diagnoses, they are not absolute.

Joss *et al.* [14] found no correlation between the degree of inflammation or fibrosis and the underlying etiology. The concentration of eosinophils cannot direct one to a particular diagnosis either. Bijol and coworkers [13] demonstrated that drug-induced GIN had more diffuse interstitial involvement with a higher concentration of eosinophils and neutrophils. In contrast, Javaud *et al.* [17] noted that drug-induced GIN should be considered when granulomas are present and when eosinophils are not seen in the inflamed interstitium. This difference surrounding the presence of eosinophils may reflect the timing of when biopsies are performed, the various medications implicated or the sampling bias that is present in patients with presumed AIN.

Treatment

Treatment for GIN depends on the underlying etiology. In drug-induced GIN, treatment involves withdrawal of the offending agent and usually a course of corticosteroids. The use of

corticosteroids has been supported by retrospective studies, but no prospective randomized controlled trials demonstrating its efficacy exist. Gonzalez *et al.* [10] performed a multicenter retrospective study of 61 patients with drug-induced interstitial nephritis. The most common drug offenders were antibiotics and NSAIDs, and the peak mean creatinine was 5.5 ± 3.3 mg/dL. Fifty-two patients were treated with corticosteroids 23 ± 17 days after drug withdrawal and nine did not receive corticosteroids. Steroid regimens varied between institutions, but the most common regimen involved pulsed methylprednisolone 250–500 mg intravenously for 3 to 4 days followed by prednisone 1 mg/kg/day tapered over 8 to 12 weeks. Treated patients had a significantly lower serum creatinine after follow-up, and a significantly lower proportion required hemodialysis compared with those who were not treated. Patients who did not achieve complete return to baseline creatinine with steroids tended to be older, have a higher baseline creatinine and had a delay in steroid administration of >2 weeks following discontinuation of the culprit drug. Although this study excluded patients with GIN, it is plausible that the findings could be relevant to this population, and further investigation is warranted to confirm this.

In some retrospective cases of GIN, withdrawal of the causative drug resulted in rapid improvement in renal function and thus eliminated the need for corticosteroid therapy, but this was more often the case when the inciting drug was a diuretic [3, 46, 47, 69]. Usually, patients have been treated with corticosteroids and receive 0.5–1 mg/kg/day for a mean or median duration of 1–3 months with improvement in renal function in most instances. Patients who even require dialysis may be able to ultimately discontinue dialytic support with corticosteroid therapy. In a case of vancomycin-induced GIN which was refractory to steroid therapy, cyclosporine and mycophenylate mofetil were initiated with partial recovery of renal function [6]. Thus, other immunosuppressive agents may be useful in treating this condition, but further investigation is necessary to support their use.

Patients with sarcoidosis and TINU benefit immensely from treatment with corticosteroids. Unfortunately, these patients are at higher risk of relapse after steroid withdrawal and often require a longer course of corticosteroid therapy than patients with drug-induced GIN [14]. Steroid-sparing agents such as azathioprine and infliximab have also been used in sarcoidosis [14, 70]. Patients with infection-induced GIN are treated for their infection and corticosteroids are generally not used.

Prognosis

A higher degree of tubular atrophy and interstitial fibrosis portends a poorer long-term renal prognosis [5, 34, 44]. Additional risk factors for worse outcome include a higher extent and severity of interstitial cell inflammation, oliguria or anuria, chronic NSAID use and duration of renal failure [5, 44]. The presence of granulomas confers a worse prognosis in patients with AIN as well.

Conclusions

GIN is a rare cause of acute kidney injury that is often the result of medications, infections, sarcoidosis and other rheumatologic conditions. The presence of granulomas on renal biopsy is of diagnostic significance as it can heighten suspicion for these particular entities, although histologic findings are not diagnostic of any single underlying etiology. Nevertheless, renal biopsy should be considered in patients with suspected AIN, because it can

facilitate treatment decisions surrounding the use of corticosteroids and allow for grounded prognostication.

We present a case of GIN following exposure to doxycycline. To our knowledge, this is the first association between GIN and doxycycline reported in the literature. As the use of antibiotics and other drugs continue to rise, we will probably find an increase in the incidence of GIN in our practice and in the literature. As such, an awareness of this condition is critical.

Conflicts of interest statement

None declared. The results presented in this paper have not been published previously in whole or part, including in abstract format.

(See related articles by Aleckovic-Halilovic et al. Granulomatous interstitial nephritis: a chameleon in a globalized world. *Clin Kidney J* (2015) 8: 511–515 and by Agrawal et al. Etiological diagnosis of granulomatous tubulointerstitial nephritis in the tropics. *Clin Kidney J* (2015) 8: 524–530.)

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