Etiological diagnosis of granulomatous tubulointerstitial nephritis in the tropics

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Abstract

**Background:** Granulomatous tubulointerstitial nephritis (GIN) is common due to infections, drugs or sarcoidosis. However, the cause is often difficult to establish and the studies are limited. We studied the etiology of GIN and compared the clinical and histological features and outcome in different etiologies at a tertiary care center in North India.

**Methods:** Renal biopsies from GIN cases diagnosed from January 2004 to April 2014 were retrieved. Stain for acid fast bacilli was performed in all biopsies. Etiological diagnosis was based on clinical features, extra-renal manifestations, radiology, history of drug intake and demonstration of infective agent. Tissue PCR for tubercular DNA was performed in seven biopsies.

**Results:** Seventeen GIN patients [mean age 35 ± 15 years; males 11] were identified. Tuberculosis was the commonest etiology followed by idiopathic, sarcoidosis and fungal. Both tuberculosis and sarcoidosis patients presented with subnephrotic proteinuria and raised serum creatinine. Acid fast bacilli were demonstrated in 1/9 and necrosis was demonstrated in 3/9 granulomas in tuberculosis. Tissue PCR for tubercular DNA was positive in six TB patients and negative in one sarcoidosis patient. Patients responded well to appropriate therapy.

**Conclusion:** Etiological diagnosis of GIN is essential for timely and appropriate therapy. Tuberculosis is the commonest etiology (53%) in the tropics. Necrosis in granuloma, demonstration of acid fast bacilli, blood interferon gamma release assay and urine culture is not sensitive for the diagnosis of tuberculosis in GIN. Our findings suggest that tissue PCR for tuberculosis performed in an appropriate clinical setting is useful in the diagnostic evaluation of GIN.

**Key words:** granulomatous interstitial nephritis, sarcoidosis, tropics, tubercular DNA, tuberculosis
Granulomatous interstitial nephritis (GIN) is a rare form of tubulointerstitial nephritis accounting for about 6% of all tubulointerstitial nephritis [1]. Etiologies include infections, sarcoidosis and drugs; however, quite often, no cause is discernible (idiopathic). Among infections, mycobacterial infection is the most common agent. Antibiotics and non-steroidal anti-inflammatory drugs are the usual causes for drug-induced GIN [2]. Rarely, inflammatory bowel disease including Crohn’s disease has also been reported as the cause of GIN [3, 4].

Studies from the USA, Europe and the UK suggest idiopathic, sarcoidosis and drug-induced etiologies as the most common etiologies of GIN [5, 6]. Tuberculosis (TB) is uncommon in the studies from the West. However, in India, being endemic for TB, there are reports suggesting tuberculosis as the commonest etiology [7, 8]. However, diagnosing TB promptly and accurately remains a major challenge and is even more difficult in extrapulmonary TB as the tests available have poor sensitivity and specificity. Smear microscopy has low sensitivity while culture is time-consuming and has poor sensitivity in paucibacillary specimens. Nucleic acid amplification tests are the most suitable choices for the identification of Mycobacterium tuberculosis with a high degree of sensitivity and specificity [9].

The treatment outcome in GIN is variable, depending on the stage and cause of the disease. Chronic GIN has a poor renal outcome [10].

The study was performed to study the etiology of GIN and to compare the clinical and histological features, associated conditions, treatment and outcome in different etiologies during a 10-year period at a tertiary care center in North India. This is the first study suggesting the utility of tissue PCR for tuberculosis in the diagnostic evaluation of GIN.

**Subjects and methods**

Renal biopsies diagnosed as GIN from January 2004 to April 2014 in the Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India were retrieved. Evaluation of renal biopsies by light microscopy was performed on routine histochemical stains [hematoxylin and eosin, periodic acid Schiff (PAS), Mason trichrome and periodic acid silver methenamine]. GIN was defined as interstitial nephritis with one or more aggregates of epithelioid histiocytes with or without necrosis or multinucleate giant cell. Periglomerular granulomatous reaction seen in crescentic glomerulonephritis was excluded. The granulomas were evaluated for presence or absence of necrosis, distinct lymphocyte cuff, to outline whether well-circumscribed or non-circumscribed and for calcification and asteroid bodies. Direct immunofluorescence for immunoglobulins and complements was performed on cryostat sections of all renal biopsies. Semiquantitative scores were assigned for the degree of tubular (infiltration of tubular epithelium by inflammatory cells) and interstitial inflammation, tubular atrophy and interstitial fibrosis as 1 (<25%), mild; 2 (25–50%), moderate; and 3 (>50%), severe, according to the percentage of renal biopsy core involved.

Ziehl Neelsen (ZN) stain for acid fast bacilli (AFB) was performed in all biopsies; CSM (chromic acid silver methenamine) stain for fungus was performed when required. Etiology of GIN was discerned based on clinical features, history of drug intake, extra-renal manifestations, radiology, culture reports, investigations, histology and demonstration of AFB/fungus. AFB demonstrated in simultaneous fine needle aspiration cytology of lymph node was noted for establishing a diagnosis of tuberculosis. Retrospectively, multiplex PCR for tubercular DNA on renal biopsy tissue from cryostat sections was performed in seven cases using protein b, MPB 64 and IS6110 primers directed against M. tuberculosis complex according to the protocol described earlier [11].

The correlation between clinical and histological features was studied using the Student t-test and Chi-square tests as appropriate.

**Results**

### Clinical data and etiology

Seventeen renal biopsies were diagnosed as GIN from January 2004 to April 2014. Most of the patients were in the third to fifth decade [mean 35 ± 15 years; range 21–74] with a male-to-female ratio of 11.6. None of the patients were in the pediatric age group. The clinical features are given in Table 1.

The etiology in most of the patients was tuberculosis (n = 9; 52.9%) followed by idiopathic (4; 23.5%), sarcoidosis (n = 3; 17.6%) and fungal (n = 1; 5.9%).

A diagnosis of tuberculosis was made after demonstration of AFB in renal biopsy (n = 1) or on fine needle aspiration smears from the enlarged cervical lymph nodes in four patients. Clinical features and radiology were useful in making a diagnosis in the rest of the patients. Multiplex PCR for tubercular DNA in renal biopsies was performed in six patients and was positive in all (Figure 1). It was negative in the case of sarcoidosis. The patients with tuberculosis presented with advanced (n = 7) to mild renal failure (n = 2) and subnephrotic proteinuria (Table 1). Respiratory symptoms were present in three and hypertension was present in six patients. On histology, AFB was seen in only one renal biopsy in a patient on steroids. Necrosis in the granuloma was noted in three biopsies (Table 2). Blood interferon gamma release assay (QuantiFERON-TB Gold) for tuberculosis performed in six was positive in one patient. Urine culture for AFB was negative in all.

All four patients with idiopathic GIN gave no significant history of drug intake. Two patients in the idiopathic category presented with nephrotic syndrome and were diagnosed on light microscopy and immunofluorescence as minimal change disease. One patient had acute tubular injury due to preeclampsia and post-partum bleeding. One patient had moderate renal failure and subnephrotic proteinuria and history of hypertension.

All three patients of sarcoidosis had respiratory symptoms. High-resolution computed tomography of the chest showed reticular opacities in lung fields and bilateral hilar nodules, showing focal calcification. Multiplex PCR for tubercular DNA was negative in a renal biopsy with sarcoidosis (Figure 1). Two patients with sarcoidosis presented with advanced renal failure and one patient presented with acute kidney injury with moderate renal failure. Proteinuria was subnephrotic in all patients.

No significant difference was found in age, serum calcium, serum creatinine and proteinuria in tuberculosis and sarcoidosis (P > 0.05) (Table 1). Idiopathic GIN was significantly less likely to present with renal failure when compared with tuberculosis and sarcoidosis (P = 0.004) (Figure 2).

### Renal histology

Renal biopsies showed interstitial granulomas associated with variable mononuclear to mixed inflammatory cell infiltrate, tubular atrophy and interstitial fibrosis (Table 2). The mixed inflammatory infiltrate was composed of lymphocytes, plasma
cells, histiocytes, neutrophils and eosinophils. Acid fast bacilli (n = 1) and caseous necrosis (n = 3) were found only in biopsies with tuberculosis-associated GIN (Figure 3). None of the other histological features were useful in reaching an etiological diagnosis in GIN (Table 2). Well-circumscribed discrete ‘naked’ granulomas as typically described in sarcoidosis were not seen on renal biopsies (Figure 3). Fungal hyphae were demonstrated in the granulomas in one biopsy. The patient with fungal granuloma had acute chronic pyelonephritis with advanced renal failure. Histology showed focal cortical necrosis, fragmented irregular broad fungal hyphae within the cytoplasm of giant cells and in the interstitium associated with dense mixed inflammation and angioinvasion (Figure 3). The histomorphology of the fungal hyphae was suggestive of *Zygomycetes* species. Fungal culture was not performed.

### Treatment and follow-up

Seven of the nine patients diagnosed as TB were on hemodialysis at the time of diagnosis. Seven received anti-tubercular treatment (ATT) and two were lost to follow-up. Corticosteroids were added in six patients who did not show significant improvement in renal function after 4 weeks of treatment. Of the seven patients who received ATT, four patients became dialysis-independent after a mean duration of 2.5 months; one who received a renal transplant was stable after a follow-up of 14 months and one died due to renal failure after 10 months while one patient was lost to follow-up.

All three patients of the sarcoidosis group and two patients in the idiopathic group presenting as nephrotic syndrome received corticosteroids. Two of the patients with sarcoidosis were on hemodialysis at diagnosis. On follow-up, one patient remained dialysis-dependent. In the idiopathic group, only one patient with hypertension had moderate renal failure requiring hemodialysis at presentation. On follow-up, this patient became dialysis-independent after administration of antihypertensives and supportive therapy. One patient of idiopathic GIN with acute tubular injury was lost to follow-up. One patient with fungal GIN required hemodialysis at presentation. He received antifungal therapy and became dialysis-independent.

### Discussion

GIN is a rare diagnosis on renal biopsies accounting for 0.3 to <1% of all renal biopsies performed [3, 6]. We describe our experience of 17 cases of GIN over a 10-year period from a tertiary care center in North India. GIN accounted for <0.5% of all renal biopsies performed during this period at our institute.

The cause of GIN has to be investigated as it has definite therapeutic implications. The etiology of GIN has geographic...
variations. Studies from the UK, Europe and the USA have reported sarcoidosis, drug-induced and idiopathic etiology as the most common cause. In one of the largest series of GIN from Glasgow, drug-induced was the most common etiology (45%), followed by renal sarcoidosis (29%) and idiopathic (10.5%). However, they did not report any case of infection-associated GIN [5].

In a similar report, Colvin et al. [3] reported 34 cases of GIN from a database of 10,383 renal biopsies at their center, and the commonest etiology was drug allergy (n = 7) followed by sarcoidosis (n = 3) and in nine, no cause could be identified. In their study, only one case of tuberculosis was reported.

This is in contrast to reports from India and southeast Asia, where TB is an important cause of GIN [7, 8]. India is one of the 22 high TB-burden countries in the world and 11% of the total TB cases diagnosed in 2013 were from India [12]. We found tuberculosis as the most common (53%) cause of GIN, followed by idiopathic (23.5%), sarcoidosis (18%) and fungal (5.9%) etiology. A previous report from India has also shown tuberculosis as the most common (64%) etiology of GIN [7].

Renal involvement in mycobacterial infection occurs due to hematogenous spread from a primary focus most commonly in the lungs. Tubercular interstitial nephritis with no extra-renal involvement is often difficult to diagnose. A clinical suspicion based on patient demographics, systemic symptoms and clinical presentation is important. Symptoms related to renal involvement appear quite late in the course of the disease, when chronic damage has already been done. The urine culture is usually negative, unless bacilli are shed in urine. Renal biopsy is not useful as granuloma may be missed and if present, may not show typical features of necrosis and presence of acid-fast bacilli. This study shows a lack of sensitivity of caseous necrosis and AFB staining in renal biopsies for determining the etiology of GIN. The utility of molecular tests for the detection of tubercular DNA has been documented in several studies and has a higher sensitivity and specificity for the diagnosis of tubercular infection [9]. In this study, we performed multiplex PCR for the detection of mycobacterial proteins in renal tissue which helped in making an etiological diagnosis of GIN. This is the first study in the literature, documenting the utility of molecular tests in GIN.

The other causes of GIN include sarcoidosis, drugs and other infections. IgG-4-related disease is increasingly recognized as a cause of tubulointerstitial nephritis. However, granulomas are not a feature of IgG-4-related tubulointerstitial nephritis [13].

Sarcoidosis is a systemic disorder of unknown etiology characterized by the presence of non-caseating granulomas in the affected organs. The prevalence of tubulointerstitial nephritis (TIN) in sarcoidosis varies from 7 to 27% [14, 15]. Isolated involvement of the kidney with no pulmonary disease has occasionally been reported [16–18]. Renal sarcoidosis can present histologically as granulomatous or non-granulomatous TIN [19]. GIN is the most typical histological finding. Historically, sarcoid granuloma is described to be ‘naked’ with no cuff of inflammatory cells with presence of asteroid bodies and calcification. In our study,
none of the biopsies with sarcoidosis showed such features. The only useful feature to distinguish from tubercular granuloma was the absence of necrosis. However, this feature was not useful in differentiating idiopathic GIN from a sarcoid granuloma.

There are currently no guidelines available for treatment of renal sarcoidosis. Azathioprine or mycophenolate mofetil can be used in renal sarcoidosis patients with a failure or a contraindication to corticosteroids or who require a high maintenance dose of corticosteroids [20]. TNF-alpha inhibitor is also useful in steroid-resistant sarcoidosis or in patients who develop severe steroid toxicity [20].

Reports suggest that the improvement in renal function in sarcoidosis correlates with the degree of hypercalcemia at presentation and complete response to corticosteroid therapy within 1 month of therapy and inversely correlates with the initial histologic fibrosis score [19].

The drugs causing GIN are antibiotics, non-steroidal anti-inflammatory agents and proton pump inhibitors [3, 21]. Other agents include tumor necrosis factor alpha inhibitors, prokinetic agents, intra-vesical BCG therapy for bladder cancer, heroin abuse, the anti-epileptic agent carbamazepine, anticonvulsant phenytoin, and all-trans retinoic acid [1, 2, 4, 5, 20, 22–29]. Some of the antibiotics reported to cause GIN include gentamycin, vancomycin, cefuroxime, clarithromycin, nitrofurantoin and ciprofloxacin [3, 30]. The pathogenesis of drug-induced GIN involves a delayed-type hypersensitivity reaction. In a study of 22 cases of drug-induced interstitial nephritis, Vanhille et al. [31] reported granulomas in eight (36%) renal biopsies. No case of drug-induced GIN was identified in our study. Though no history of drug intake could be elicited in our patients before the onset of renal disease, this possibility cannot be completely ruled out in idiopathic cases.

Rarely, infections other than tuberculosis may also cause GIN. GIN secondary to fungal infection including Histoplasma, Candida and Rhodococcus has been reported [32–34]. One patient in our study had undergone renal biopsy with a clinical diagnosis of acute interstitial nephritis. Renal biopsy showed fungal hyphae with histological features suggestive of Zygomycetes. No predisposing factor or immunosuppressed state was identified.

Despite clinical history, appropriate investigations and histology, an etiology cannot be defined in some cases which are labeled as ‘idiopathic GIN’. Idiopathic GIN accounts for 8–50% of GIN in different studies [1, 3, 5, 6]. In our study, about one-fourth of GIN was idiopathic. There was no history of drug intake. It was associated with nephrotic syndrome due to minimal change disease in two cases. One of the patient, a known hypertensive, presented with moderate renal failure and subnephrotic proteinuria. One of our pre-eclamptic patients had idiopathic GIN associated with acute tubular injury due to post-partum bleeding. There are occasional previous reports of idiopathic GIN presenting as acute kidney injury [35].

GIN is an uncommon cause of renal allograft dysfunction. Ozdemir et al. [36] reported tubulointerstitial nephritis in 8% (23/280) of patients presenting with graft dysfunction, three of which had GIN. Meehan et al. [37] reported GIN in 0.6% of graft renal biopsies. We did not find any case of GIN in graft biopsies during the study.
period. The etiologies of GIN in the renal allograft include infections due to immunocompromised state and antibiotics [37]. Mycobacteria and fungi-like candida are the main etiologic factors for infection-related GIN in renal transplants [3].

Renal survival in GIN is dependent on the degree of renal dysfunction at presentation and the grade of chronic changes on histology. The insidious onset and non-specific constitutional symptoms of genitourinary tuberculosis often lead to delayed diagnosis and rapid progression to a non-functioning kidney. Determination of the etiology of GIN is important for appropriate therapy. In India, TB is the most common cause of GIN. AFB in granuloma on renal biopsy is rare, seen only in an immunocompromised patient. Clinical suspicion, chest radiology and necrotizing granuloma, if present are useful in distinguishing TB from sarcoidosis. Multiplex PCR for TB DNA in renal tissue is supportive for the diagnosis of TB GIN. GIN presents late with advanced disease. In high-risk populations, a low threshold of suspicion might lead to timely diagnosis and initiation of treatment, thus preserving renal function.

**Conflict of interest statement**

None declared.

(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 Shah et al. Granulomatous interstitial nephritis. Clin Kidney J (2015) 8: 516–523.)

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