



## ORIGINAL ARTICLE

# Single-centre experience of granulomatous interstitial nephritis—time for a new approach?

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## Abstract

**Background:** Differentiating between renal-limited sarcoidosis and tuberculosis (TB) infection as a cause of granulomatous interstitial nephritis (GIN) can be difficult. This series compares clinical features and response to treatment between the different underlying aetiologies in order to propose a management algorithm for GIN to assist with diagnosis and treatment.

**Methods:** This retrospective study reports on all patients presenting with a histological diagnosis of GIN between 2000 and 2012 at our unit.

**Results:** Twenty-one patients were identified, 57% were male and the mean age was 53 years. Eight cases were associated with sarcoidosis with evidence of extra-renal disease and five with renal-limited sarcoidosis. Five patients had GIN that may have been related to TB infection or to renal-limited sarcoidosis, and three were idiopathic or drug related. All those with sarcoidosis were treated with steroids and renal function, as measured by estimated glomerular filtration rate (eGFR), improved from a mean of 24 mL/min at baseline to 37 mL/min at 1 year. Baseline eGFR was 19 mL/min in those with possible TB infection. Four received steroids as well as anti-TB drugs. Anti-TB therapy was delayed in four patients by a mean of 22 months due to difficulties in diagnosis. Two patients with TB developed end-stage kidney disease and the remaining three patients had a mean eGFR of 28 mL/min at 1 year.

**Conclusions:** This series represents the largest cohort of patients with GIN in the UK and supports previous findings that patients with sarcoid have a favourable outcome with steroid treatment. Those with TB have an inferior prognosis, perhaps due to delayed diagnosis. We suggest an algorithm when investigating a diagnosis of GIN with the aim of expediting diagnosis and considering a trial of anti-TB therapy in order to prevent deterioration of renal function.

**Key words:** chronic kidney disease, granulomatous, interstitial nephritis, sarcoidosis, tuberculosis

## Introduction

Granulomatous interstitial nephritis (GIN) is a rare histological diagnosis found in 0.5–0.95% of native renal biopsies [1]. Underlying aetiologies include drug reactions, infections (particularly mycobacterial), sarcoidosis and granulomatosis with polyangiitis. However, frequently a cause cannot be established. Differentiating between these aetiologies using histological

features is difficult and therefore diagnosis often depends on clinical presentation and the presence (or absence) of extra-renal disease. The presence, for example, of bilateral hilar lymphadenopathy and/or non-caseating granulomas elsewhere in the body indicates that GIN may be due to sarcoidosis.

In 2013, there were 0.8 million new cases of extra pulmonary tuberculosis (TB) worldwide [2], mainly reported in patients of

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Asian and Black ethnicity [3]. The genito-urinary tract is the second most common site for non-pulmonary TB, accounting for 15–20% of such cases [2]. The classical presentation of genito-urinary TB is of sterile pyuria and systemic symptoms with characteristic features on radiological imaging and caseating granulomas in renal biopsy specimens [4]. However, in a number of patients, renal TB results in kidneys that appear radiologically normal with few systemic symptoms and the finding of GIN on biopsy [5, 6]. Renal decline, in this instance, can be insidious and remain unnoticed for several years [7]. Therefore, the diagnosis of TB can be elusive, leading to misdiagnosis and inappropriate treatment with steroids.

Renal outcome is largely dependent on the underlying aetiology. Sarcoidosis has a better prognosis, compared with TB, with the majority responding to steroid treatment [5, 8, 9]. In one series, 36% patients required initiation of renal replacement therapy (RRT) within 6 months of diagnosis of TB-related GIN [5] contrasting with 4% of patients who developed end-stage renal disease with sarcoidosis-related disease [10]. Patients with TB are often identified late in the disease course and this may explain the inferior outcome. Earlier identification and treatment can improve outcomes in this group [5]. As the incidence of TB in London is much higher, at 35.5 per 100 000 compared with 12.3 per 100 000 population for the rest of the UK (2013 data), TB remains an important differential for GIN in renal units, such as ours, serving the London population [11].

Previous series, from the UK, France, Germany and India, have described the natural history of GIN and the response to treatment but relatively few of these patients, in the UK, had TB infection [1, 5, 8–10, 12–16]. Underlying causes of GIN vary according to geographical location with TB accounting for just over half of all cases from a series from India versus no TB infection from a Glasgow series [12, 16]. The aim of our study, therefore, was to examine the difference in disease course between the underlying aetiologies focusing on the comparison between those with a GIN attributable to TB infection and other identifiable diagnoses. From our experience, we have suggested a pathway for investigation of GIN to promote earlier detection of TB that may lead to improved outcomes for these patients.

## Materials and methods

Patients with a histological diagnosis of GIN from January 2000 to April 2012 were identified from our database at King's College Hospital for this retrospective study. All biopsies demonstrating interstitial nephritis and the presence of one or more granulomata were included in the analysis. A full clinical history and examination was undertaken for all patients in this series. This incorporated specific questions regarding constitutional symptoms such as night sweats and weight loss as well as taking a comprehensive drug history (which included over the counter and herbal remedies). HIV testing was not routinely performed but we have reported the results where available. All patients had a chest X-ray performed.

The following data were collected for each patient; serum creatinine, estimated glomerular filtration rate (eGFR) (calculated by Modification of Diet in Renal Disease formula [17]), proteinuria, serum angiotensin-converting enzyme (ACE), serum calcium at the time of presentation, along with demographic details and characterization of extra-renal features, when present. The biopsy samples were examined by standard methodology that included light microscopy (staining with haematoxylin and eosin, periodic acid-Schiff reaction, silver methenamine and trichrome stains) and immunohistochemistry (antibodies to IgA, IgG, IgM, C1q, C3,

C4 routinely used). In the presence of granulomas, further analysis with Ziehl-Neelsen and Gomori methenamine silver stains were performed. However, TB cultures and PCR were not routinely undertaken due to insufficient material.

For the purposes of analysis, the patients were divided according to the clinical diagnosis determined by the clinicians: GIN related to sarcoidosis (with extra-renal features of the disease), renal-limited sarcoidosis, TB infection and/or renal-limited sarcoidosis, or drug-related/idiopathic. Details of treatment initiated for GIN were recorded including dose of steroid initially prescribed and duration of therapy, as well as the requirement for RRT. The effect of treatment was assessed by changes in eGFR at 1, 6 and 12 months and at the last clinic visit, and compared using Student's *t* test.

## Results

Twenty-one patients with GIN were identified, 38% were of black ethnicity, 57% were male with a mean age 53 years (range: 19–73). Eight (38%) cases were associated with sarcoidosis with evidence of extra-renal disease and five (24%) with renal-limited sarcoidosis, one (5%) case was related to medication and two (10%) were idiopathic. Five (24%) further patients with GIN were also diagnosed with TB during follow-up. However, in only one case was the GIN attributed to TB infection at presentation.

The mean duration of follow-up was 52 (range: 0–135). Two (10%) patients died during the follow-up period. Table 1 lists the clinical features, including the results of HIV tests where available and relevant histopathological findings of the cases. Table 2 lists the laboratory results with the presentation for different aetiologies.

### Underlying renal diagnosis

#### Sarcoidosis with extra-renal disease

Eight patients diagnosed with renal sarcoidosis had evidence of extra-renal disease. Three patients had a diagnosis of sarcoid, confirmed by histological examination of the affected organ, prior to presenting with renal dysfunction. The remaining five patients were found to have non-renal manifestations of sarcoid at or soon after presentation with kidney disease (Table 1). Respiratory disease was the most common extra-renal feature. All patients were treated with prednisolone (median dose 30 mg) for a mean of 47 months (range: 7–131). In addition, steroid-sparing agents, such as azathioprine or mycophenolate mofetil (MMF), were administered in four patients. At presentation mean eGFR in this group was 26 mL/min and this increased to 39 mL/min at 1 year and 48 mL/min at last follow-up (mean 69 months, range: 8–135). Mean proteinuria at baseline was 0.68 g/day (range: 0–1.8), falling to 0.1 g/day (range: 0–0.9) at 1 year. Mean serum ACE at baseline was 101 U/L (range: 40–258), falling to 24.5 U/L (range: 4–68) at 1 year.

#### Renal-limited sarcoidosis

Five patients were diagnosed with renal-limited sarcoidosis. All patients were treated with steroids; median dose was 40 mg for mean of 57 months (range: 15–111). Four of the five patients responded to treatment as mean eGFR at presentation was 21 mL/min, which improved to 35 mL/min at 1 year and 35 mL/min at the end of follow-up (mean: 64 months, range: 15–113). One patient experienced deteriorating renal function despite treatment. He was presented with an eGFR of 32 mL/min falling to 15 mL/min after 101 months of follow-up. However, this patient did not attend clinic appointments regularly and non-compliance with therapy was suspected. Plain chest

Table 1. Clinical data and histological findings for the patients in study

Age/sex	Ethnicity	Diagnosis	% fibrosis on biopsy	HIV status	Extra-renal features	Treatment	eGFR at diagnosis mL/min	1 year eGFR mL/min	Latest eGFR mL/min (follow-up interval, months)
50 F	White	Sarcoid	10	N/A	Skin sarcoid	Steroids	17	35	50 (87)
52 M	White	Sarcoid	30	N/A	Uveitis, spine, intestine	Steroids and MMF	46	47	66 (85)
66 F	Black African	Sarcoid	80	N/A	Erythema nodosum, bi-hilar lymphadenopathy	Steroids	24	24	42 (131)
45 F	Black African	Sarcoid	25	N/A	LN +ve, uveitis, + myocarditis	Steroids	39	40	40 (12)
49 F	Unknown	Sarcoid	30	N/A	Bi-hilar lymphadenopathy	Steroids	11	52	76 (135)
38 M	Pakistani	Sarcoid	25	N/A	Restrictive defect on lung function	Steroids + azathioprine	44	55	68 (67)
66 F	White	Sarcoid	30	N/A	Raised serum ACE + calcium, uveitis	Steroids, azathioprine, MMF	11	21	22 (26)
71 M	White	Sarcoid	40	N/A	Calcified granuloma on CXR	Steroids	16	N/A	17 (8)
69 M	Black Caribbean	Renal-limited sarcoidosis	100	N/A	Raised serum ACE + calcium	Steroids	17	35	44 (66)
68 M	White	Renal-limited sarcoidosis	25	N/A	Nil	Steroids	11	21	18 (deceased 113)
52 M	Black African	Renal-limited sarcoidosis	35	N/A	Nil	Steroids	32	25	15 (101)
43 M	White	Renal-limited sarcoidosis	20	N/A	Nil	Steroids	37	51	56 (27)
47 M	Black	Renal-limited sarcoidosis	0	N/A	Nil	Steroids	10	41	41 (15)
41 F	Indian	TB infection and/or renal-limited sarcoidosis	100	Negative	Caseating granuloma on biopsy	Anti TB only	10	On HD	On HD (26)
60 F	Black	TB infection and/or renal-limited sarcoidosis	80	Negative	LN biopsy, granulomatous inflammation with caseation	Steroids for 5 years, then anti-TB	16	12	On HD (126)
47 M	Indian	TB infection and/or renal-limited sarcoidosis	0	N/A	Miliary TB	Steroids for 9 months then anti-TB	17	24	25 (15)
37 M	Indian	TB infection and/or renal-limited sarcoidosis	20	N/A	+ve Sputum culture of TB	Steroids for 7 months, then anti-TB	29	33	40 (21)
19 M	Black	TB infection and/or renal-limited sarcoidosis	20	Negative	LN biopsy, necrotising granulomatous inflammation highly suspicious for TB	Steroids for 2 months	23	26	17 (15 months)
73 F	White	Secondary to NSAID	50	N/A	Nil	Steroids	13	N/A	34 (9 months)
60 M	Black Caribbean	Idiopathic	0	N/A	Nil	Steroids	11	Deceased	Deceased (3 months)
54 F	Unknown	Idiopathic	20	N/A	Nil	Steroids	113	Lost to follow-up	Lost to follow-up

CXR, chest X-ray; F, female; HD, haemodialysis; LN, lymph node; M, male; N/A, not available; NSAID, non-steroidal anti-inflammatory drug.

Table 2. Biochemical data for each group at presentation

Underlying diagnosis	Mean serum ACE, µg/L (range)	Mean serum calcium, mmol/L (range)	Mean renal function (eGFR), mL/min (range)	Mean proteinuria, g/24 h (range)
Sarcoid	101 (40–258)	2.46 (2.24–2.88)	26 (11–46)	0.68 (0–1.8)
Renal-limited sarcoidosis	110 (40–194)	2.59 (2.24–3.44)	21 (11–37)	0.21 (0–0.34)
TB infection and/or renal-limited sarcoidosis	29 (7–58)	2.28 (2.03–2.46)	19 (10–29)	0.74 (0.23–1.4)
Idiopathic and drug-related GIN	41 (28–49)	2.32 (2.17–2.42)	46 (11–113)	3.15 (0.5–5.8)

radiographs did not show evidence of respiratory involvement for patients in this group.

#### TB infection and/or renal-limited sarcoidosis.

One patient with GIN was diagnosed with TB infection after the histological examination of renal tissue. The remaining four patients were initially diagnosed with renal-limited sarcoidosis, as there was no evidence of systemic disease associated with TB infection at the time of presentation and the Ziehl Neelson (ZN) stains on the kidney biopsy were negative with no evidence of pulmonary TB on chest X-ray. However, they were also diagnosed with TB at a different time point (one before the renal biopsy and three after). These patients were treated with steroids (median dose 40 mg for mean duration of 38 months, range: 7–122). Three of these patients subsequently presented with extra-renal features consistent with TB infection. Of note, these patients had a mean serum ACE of 19 IU/L (range: 7–29). Treatment of TB infection was delayed by a mean of 22 months (range: 1–60).

Three of these five patients were from the Indian subcontinent. Mean eGFR was 19 mL/min (range: 10–29) and proteinuria was 0.7 g/day (range: 0.23–1.4) at presentation. Two patients developed end-stage kidney disease almost immediately after presentation to the renal department and the remaining three patients had a mean eGFR of 28 mL/min (range: 24–33) at 1 year and 27 mL/min (range: 17–40) at the end of follow-up (mean 41 months, range: 15–126).

In the first case, a 41-year-old Indian female presented with end-stage renal disease. She was diagnosed with TB infection after histological analysis of a nephrectomy sample performed for a suspicious solid lesion and treated with anti-TB therapy.

In the second case, a 60-year-old black female, the initial kidney biopsy showed 80% fibrosis and the patient started dialysis soon after despite treatment with steroids. Given the degree of fibrosis, it is perhaps not surprising that her renal function did not recover. Five years later she presented with fevers and lymphadenopathy and following a biopsy of a lymph node, a diagnosis of TB infection was made and appropriate therapy was commenced.

In the third case, a 47-year-old Indian male was treated with steroids for GIN for 9 months, which resulted in some improvement of renal function (eGFR at baseline 17 mL/min and at 9 months 26 mL/min). He then presented with respiratory symptoms and was found to have miliary TB infection.

In the fourth case, a 37-year-old Indian male developed a cough and fever and TB was isolated from sputum 18 months after original diagnosis and treatment with steroids for his GIN.

In the final case, a 19-year-old black male had been fully treated 2 years previously for TB infection isolated from an axillary lymph node. He then presented with renal impairment and a kidney biopsy showed GIN. This was attributed to renal-limited sarcoidosis as there were no systemic features to suggest TB infection and urine cultures were negative. He was therefore not treated with anti-TB therapy. However, his renal

function continued to decline despite steroid therapy and he is currently preparing for dialysis.

#### Idiopathic and drug-related GIN.

The idiopathic and medication-related cases of GIN presented with a mean eGFR of 46 mL/min (range: 11–113) and proteinuria 3.15 g/day (range: 0.5–5.8), and all commenced steroid therapy. One patient had GIN secondary to the use of a non-steroidal anti-inflammatory drug whereas the other two had no specific cause attributed to the finding. Two patients in the group were only followed up for 1 month so meaningful data on changes in renal function over time are not available. During the first year, one patient died following an unexpected cardio-respiratory arrest.

#### Treatment.

Twenty out of twenty-one patients were treated with steroids. Mean duration of treatment was 36 months (range: 3–132). As expected, eGFR for patients with possible TB infection did not improve after treatment with steroids ( $P = 0.6$ ). However, for those with extra-renal sarcoid, there was an improvement in eGFR from a mean of 26 mL/min to 48 mL/min ( $P < 0.05$ ) and from 21 mL/min to 35 mL/min for those with renal-limited sarcoidosis ( $P = 0.02$ ). Figure 1 shows the response to treatment of the three main underlying aetiologies and shows that an improvement in eGFR is evident after 1 month for those with sarcoid.

## Discussion

Our cohort of 21 patients with GIN represents the largest series reported in the UK and provides an opportunity to propose an investigative pathway for those patients diagnosed with GIN. This is needed as our data have suggested that patients with TB infection are exposed to unnecessary steroids and diagnosis can be delayed. Those patients with sarcoid-related GIN exhibited significant improvement in eGFR with steroid therapy, in keeping with previous reports.

TB may have been implicated in 24% of our cases but the diagnosis of TB was delayed in 80% of these due to an absence of constitutional symptoms and lack of TB isolation from the renal biopsy specimens. A similar experience was reported by Chapagain et al. who noted that 47% of patients with TB-related GIN had no symptoms of TB at the time of renal biopsy, although 63% of these did report weight loss in the preceding months [5]. We cannot be certain that TB infection was responsible for the GIN found in our patients. In Cases 2, 3 and 4, TB infection may have represented primary infection not related to the GIN diagnosed previously. These patients were at increased risk of TB infection due to end-stage renal disease, history of corticosteroid treatment without isoniazid prophylaxis and ethnicity. However, it is also possible that the GIN was related to primary TB infection that then entered a latent phase with subsequent reactivation years later. Furthermore, the lack of steroid responsiveness in Cases 2, 4 and 5 is not in keeping with

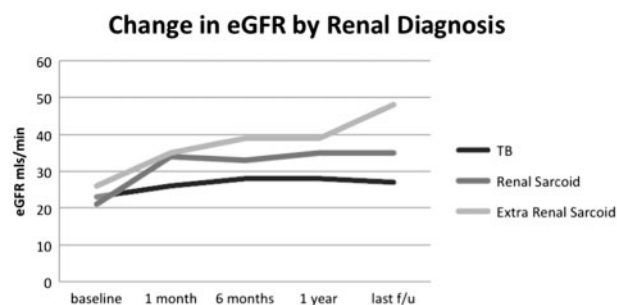


Fig. 1. Change in eGFR versus time since diagnoses according to different underlying aetiologies. TB data censored for the two patients who developed end-stage renal failure.

natural history of treated renal-limited sarcoidosis. In the third case, treatment with steroids led to some improvement in renal function, which may not be consistent with TB GIN [5]. However, this patient was later diagnosed with TB and therefore we remain concerned that in these cases the diagnosis and treatment of TB may have been significantly delayed resulting in a missed opportunity to preserve renal function.

In Case 5, diagnosis of TB infection predated detection of GIN. This case highlights another issue with differentiating between the two diseases as TB infection can trigger a later diagnosis of sarcoid [18].

These cases emphasize the efforts required to diagnose renal TB infection and distinguish it from renal-limited sarcoidosis, and support the need for an algorithm for the clinical management of GIN.

We believe that further tests may be useful to establish a diagnosis of TB infection, in particular PCR examination of the biopsy for mycobacterial DNA. In a recent series from India, PCR testing was positive in 67% of cases of TB infection with only 11% isolating acid-fast bacilli [16]. These data, however, must be contrasted with the findings of Chapagain *et al.*, where none of their patients had a positive PCR test [5].

Therefore, although PCR testing may be diagnostic, a negative result does not preclude TB infection. A negative PCR result may not be surprising as it has been speculated that TB does not always affect the kidney directly but can cause a GIN via immune-mediated pathways and therefore it would not be possible to detect TB DNA in renal tissue [6]. Over the last decade, interferon gamma release assays (IGRAs) have been introduced into clinical practice as a means of diagnosing TB infection. These detect the release of interferon gamma from T-cells in response to mycobacterial antigens [19]. Although useful for excluding TB, the test cannot distinguish between active and latent TB [20]. Therefore, a positive IGRA does not confirm that the GIN is caused by TB infection, it may just represent previous TB infection. However, if the IGRA test is positive and the patient has risk factors for TB infection, for example, being of Asian or Black ethnicity, having end-stage renal disease and a history of corticosteroid treatment without isoniazid prophylaxis along with a poor response to steroids started for renal sarcoidosis, then perhaps a trial of anti-TB therapy is justified. The use of anti-TB medication must be weighed against their risks, which include haematological, hepatic and ocular toxicity [3, 21]. Hepatotoxicity severe enough to stop the offending drug or raise alanine transaminase five times above the normal range occurs in 7% of patients being treated with at least two anti-TB drugs [3].

Consistent with the reports of others, our TB patients experienced a poor renal outcome. This may be due to the fact that

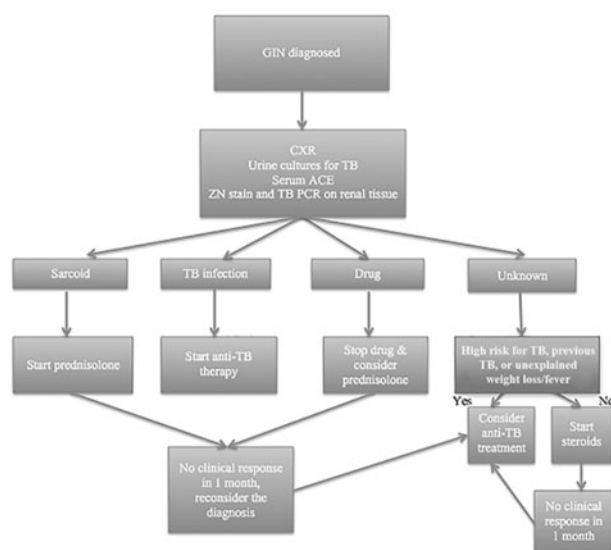


Fig. 2. Suggested algorithm for the investigation of GIN. CXR, chest X-ray.

anti-TB treatment was delayed by a mean of 22 months. We need to consider how these patients can be identified earlier if they have no symptoms of TB and negative tests on biopsy. We suggest the algorithm in Figure 2 when investigating a diagnosis of GIN. If features of extra-renal sarcoidosis or TB infection are present then these patients should be treated with either steroids or anti-TB therapy. If a new drug has commenced then this should be withdrawn and steroids prescribed. If no obvious cause is identified then if considered high risk for TB or has a previous history of TB or has unexplained weight loss or fever, then consider a trial of anti-TB therapy [22]. For patients initially diagnosed with a renal-limited sarcoidosis or drug-related GIN, no improvement in eGFR after 1 month of treatment should prompt the clinician to reconsider the diagnosis and consider anti-TB treatment. TB prophylaxis with isoniazid needs to be considered when prescribing a course of steroids in high risk patients with sarcoidosis or drug-related GIN [23].

The limitations of this study include the retrospective nature of data collection and the relatively small sample size. However, as previously stated GIN is a relatively rare histological diagnosis and this study represents the largest series of GIN patients from the UK. A further limitation is the small proportion of patients with HIV test results. However, given the long-term follow-up available for these patients within our unit and the fact that none of them has presented with HIV-related symptoms or diseases, we think that HIV was highly unlikely to be involved in any of our cases.

This series describes the clinical outcomes for those patients with GIN. TB was likely to be the cause of the lesion in nearly a quarter of our patients but there may be significant delays in confirming this diagnosis. Nephrologists should have a high index of suspicion for TB in those presenting with an otherwise unexplained cause for their GIN, especially if they have risk factors for infection or a poor response to steroid therapy. Earlier identification of this infectious aetiology may lead to better renal outcomes for this group of patients.

### Conflict of interest statement

None declared.

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