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Leading European Nephrology

*Clinical Kidney Journal*, 2015, vol. 8, no. 5, 511–515

doi: 10.1093/ckj/sfv092
Editorial Comment

## Granulomatous interstitial nephritis

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# Granulomatous interstitial nephritis: a chameleon in a globalized world

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**Key words:** granulomatous interstitial nephritis, renal biopsy, tuberculosis

## Introduction

Two articles in this issue deal with granulomatous acute interstitial nephritis (GIN), a rare disorder seen in 0.5–0.9% of native and 0.6% of transplant renal biopsies [1]. In the first article, Agrawal and co-workers report 10 years of experience with GIN in a tertiary centre in India [2]. In contrast to the experience from Western countries, tuberculosis accounted for more than half of cases. The authors emphasize the challenge of making the diagnosis and recommend a high degree of suspicion [2]. In a second article, Shah and colleagues from the USA [3] review GIN and also highlight current challenges in describing the interesting case of a 69-year-old man with GIN ascribed to doxycycline in whom a positive quantiferon test was received and who eventually died from multi-organ failure. Without autopsy we will never know whether he actually had tuberculosis but their case also reminds us that even with sophisticated testing the cause of GIN remains unclear in a proportion of patients. In this comment, we reflect on both articles and provide some context with an emphasis on pathology and disease patterns worldwide, pitfalls and the diagnostic approach in clinic.

## Pathology and cells

First described in 1679, granulomas are the result of a complex interaction of inflammatory mediators orchestrated by T cells in response to a persistent stimulus [4, 5]. Granuloma formation is best understood in sarcoidosis, where secretion of tumour necrosis factor (TNF) by macrophages is followed by a complex interplay of T helper (Th) 1 and Th17 cells with synthesis of interleukin-6 (IL-6), IL-12, IL-18, IL-23 and transforming growth factor (TGF)-β [6]. These cytokines stimulate macrophages, resulting in functional changes [7] and maturation into epithelioid cells and eventually giant cells [6, 7]. Other inflammatory cells, such as natural killer (NK) cells, which produce interferon (INF)-γ, are also involved. Glucocorticosteroids exert their beneficial effect on granulomas by repression of NF-κB-related gene transcription with lymphocyte apoptosis [6]. Until recently, the granuloma was seen as a static structure but research in tuberculosis has revealed that granulomas are highly dynamic [4]. An improved understanding of granuloma formation and pathways may reveal useful therapeutic targets for the future [4].

Bijol and Viero looked extensively at the specific pathology of GIN [5, 8]. Granulomas in GIN may be isolated or extensive; they can be well-formed or ill-defined, with or without concomitant necrosis. Bijol *et al.* noted that most of the inflammation was present in the cortico-medullary junction or outer medulla [8]. Occasionally granulomas are orientated around vessels [5]. Of note, between 30.4% [8] and 93% [5] have an additional unrelated histological lesion on biopsy. Viero *et al.* also characterized the type of cells involved in GIN in 10 of 12 renal biopsies with GIN. Not surprisingly, macrophages and T lymphocytes were the most abundant cells, and the presence of activated cells paralleled the intensity of the inflammation. B lymphocytes were less abundant, and absent in 20% of biopsies [5]. Human leukocyte antigen (HLA)-DR antigens were also expressed by proximal tubular and endothelial cells.

## Causes and associated disorders

Possible causes of GIN include mainly drugs, immune-mediated diseases (mainly sarcoidosis) and infection, in particular tuberculosis. Shah and co-workers in this issue of the journal [3] and previously Joss and colleagues [1] review causes and provide exhaustive lists. One does wonder though about the remaining 10% or so of GIN cases labelled as 'idiopathic'. Is it possible that

**Received:** August 28, 2015. **Accepted:** August 31, 2015

further as yet unidentified infectious agents cause GIN? Viruses are clearly capable of inducing GIN both in humans and in animals. Porcine circovirus causes GIN in pigs [9]. Furthermore, is it possible that insidious cases of tuberculosis [10] are currently overlooked? Others have emphasized that undiagnosed cases of tuberculosis may be lurking among the many patients with 'end-stage renal failure of unknown origin' documented in clinic letters and renal registries alike [10]. There is also evidence of over-representation of idiopathic interstitial nephritis in the Indian population in the UK where tuberculosis is more prevalent [11]. The authors attempted to exclude tuberculosis with urine testing for acid fast bacilli and Ziehl-Neelsen staining of biopsies, but acknowledge that these tests may lack sensitivity for tuberculosis [11, 12]. A recent series from the UK reported as many as 17 cases of known tuberculosis with GIN [13]. We also need to remember that global trends of migration may make tuberculosis more common in Western countries and we should probably consider the disease more often in GIN patients from at risk populations—that is certainly a take home message from this issue of the journal. Another interesting question is whether other non-infectious environmental factors may play a role. Jha and co-workers have previously emphasized the differences in environmental risk factors for kidney disease worldwide although their discussion focussed on chronic interstitial nephritis [14]. Many natural medicines are capable of causing acute interstitial nephritis [15] and it is not inconceivable that some of the 'unexplained' cases of GIN are caused by as yet unidentified environmental factors which may well include over the counter medication or herbs.

Another interesting association of GIN is that with the immune reconstitution inflammatory syndrome (IRIS) occurring in Human Immunodeficiency Virus (HIV)-infected patients [16]. There have been numerous case reports of IRIS-GIN related to mycobacterial infection, although IRIS can also occur with non-infectious diseases. The impaired CD4+ cell function in HIV changes cytokine secretion, causing a switch from cell-mediated immunity (Th1) to humoral immunity (Th2), impairing granuloma formation. Antiretroviral treatment restores the host's ability to form granulomata, often resulting in intense 'paradoxical' reactions [17]. An equally interesting recent observation is that of GIN caused by antibodies against immune checkpoint protein used in treatment of malignant melanoma [18].

## A global view of GIN

The notion that GIN has different aetiologies on different continents is interesting in itself. Nephrologists in developed countries will probably have drugs and sarcoidosis as top of their list in terms of differential diagnosis: Remarkably, Joss and colleagues from Glasgow in the UK did not report a single infectious aetiology in their series of 18 cases of GIN reported in 2007. Similarly, Bijol and colleagues from the USA failed to detect a single case with infectious aetiology among their 14 cases with GIN reported in 2006.

In reporting tuberculosis as the predominant cause of GIN in their series from India, Agrawal and colleagues provide a worthwhile reminder that things may be very different elsewhere. Similarly, Naidu and colleagues from Hyderabad in India reported 14 patients in 2013 of whom 9 had tuberculosis and only 2 were believed to be drug-associated. There are further case series from the Indian sub-continent in addition to the paper by Agrawal in this month's edition of the journal [2]. Gupta and colleagues reported a series of 16 cases of GIN from Delhi in 2014 [19]. Interestingly their series also included two cases of GIN in a renal allograft. In their series tuberculosis was the most common cause of GIN. Similar reports from other parts of Asia are rare. Chung and co-workers from Seoul in Korea described an interesting case of GIN associated with cryptococcosis [20]. Much less is known about GIN in Africa and South America. In a large series from South Africa one of us reported a remarkable 45 cases in HIV, 73% of whom had evidence of tuberculosis [21].

Taken together, there is clearly a picture of more infection-associated GIN in developing countries and more drug-associated cases in the developed world [1, 8]. Interestingly, two studies from France [22, 23] are somewhere in between regarding the percentage of cases associated with tuberculosis and those attributed to other causes.

## Can the histopathology help with differential diagnosis?

Histological findings in GIN, whilst never specific to a particular aetiology [1, 5], may help to point the clinician in the right direction. In that sense, one message from the two papers in this issue of the journal is the importance of clinic-pathological correlation and dialogue. How can the pathologist help us? Firstly, in sarcoidosis granulomatous inflammation is usually non-necrotising, in contrast to those associated with antineutrophil cytoplasmic antibody (ANCA)-positive diseases such as granulomatosis with polyangiitis and infections such as tuberculosis [5]. Giant cells and granulomas also vary in numbers and provide some direction [1] although no pattern is absolute or diagnostic of any one aetiology [3]. Viero and Cavallo and Bijol *et al.* report that abundant granulomata are observed in GIN associated with sarcoidosis but are fewer in number when drugs are the cause [5, 8]. Moreover, the granulomas of sarcoidosis are described as 'naked' (i.e. without a rim of lymphocytes) [1] while abundant neutrophils and eosinophils, with ill-formed granulomas in a diffuse distribution, point towards a drug-induced aetiology [8]. Sarcoidosis, in an advanced stage, may be characterized by marked interstitial fibrosis [24], although in the literature varying amounts of fibrosis are seen in many different causes of GIN. Others found the presence of eosinophils not helpful in diagnosing a drug-related aetiology [1]. Immunofluorescence and electron microscopy are not usually very helpful [5].

Another challenge that the pathologist can help to address is to exclude infection as the cause of GIN. GIN related to pyelonephritis or systemic infection has been noted to have an intense inflammatory infiltrate with lymphocytes, neutrophils and plasma cells, microabscess formation, white cell casts with or without papillary necrosis and vessel thrombosis and infarction [5]. Neutrophils predominate over other cell types, but the numbers of T and B cells and macrophages are comparable to that seen in GIN from other causes [5]. Infections with mycobacterial or fungal pathogens are usually associated with necrotising granulomatous inflammation. The finding of caseous necrosis is more suggestive of tuberculosis (although this can be seen in other infections [25]). However, this was only seen in 18.7% of cases of tuberculosis-GIN in one series [13]. In some cases, the infective agent can be readily identified with special stains (periodic acid-Schiff, Masson Trichrome, Silver and Ziehl-Neelsen or Auramine) [8, 26]. However, in certain cases, necrosis is absent, and granulomas may be poorly formed and a high index of suspicion is needed. Biopsies should be examined for possible aetiologies of GIN e.g. micro-organisms (fungi, acid-fast bacilli, viral inclusions) and polymerase chain reaction (PCR) may be required for certain pathogens. Culture of fungi and mycobacteria is highly specific, but the result is often too delayed to be clinically

meaningful at the time of the biopsy. Serologic tests e.g. anti-*Histoplasma* antibodies may be helpful, but false-negative results do occur, especially early in the course of infection, and possibly more often in immunocompromised hosts [27]. Detection of fungal antigens in serum or urine allows for more rapid diagnostics, but sensitivities vary [27]. A newer point-of-care test (XPert MTB/Rif) has been developed for detection of tuberculosis, but this has yet to be studied in histological specimens.

The situation is even more difficult in the immunosuppressed patient. A recent study in HIV patients gave valuable insight in the diagnostic challenge in this particular population [21]. Infections are leading causes of GIN in these patients and in renal transplant recipients [19, 28]. Tuberculosis is not only more frequent among the immunosuppressed, but the immunosuppression may also alter the clinical picture and thereby obscure the diagnosis. This is not helped by the fact that tubulitis is a common feature of rejection and interstitial nephritis and differentiating acute interstitial nephritis from rejection in a graft is notoriously difficult.

Another aetiology one does not want to miss is surely oxalosis, and biopsies should be examined closely for crystals. Granulomas in the vicinity of vessels must be distinguished from vasculitis with granulomatous inflammation as seen in granulomatosis with polyangiitis. In all likelihood though, both oxalosis and ANCA vasculitis would eventually manifest with other signs and symptoms that would probably lead to the correct diagnosis at some stage. Finally, tubulorrhexis in acute tubular necrosis can be associated with granulomatous inflammation and must be distinguished from true GIN.

## Diagnostic approach

GIN is rarely expected as a biopsy finding and often comes as a bit of a surprise. At this point the underlying cause will be either obvious or at least likely in a sizeable proportion of patients, i.e. those with known sarcoidosis, tuberculosis or an exposure to medication within a relevant time frame. What to do if at this point the cause is still enigmatic? Based on our experience and our understanding of the literature we would suggest a stepwise (but not dogmatic) approach (Figure 1). Good dialogue with the nephropathologist should be the starting point. No histological pattern is diagnostic of any of the main causes of GIN but, as detailed above, important pointers can be obtained from the number and phenotype of granulomas and the inflammatory infiltrate. Further testing of the biopsy specimen should be discussed at this point. History-taking needs to include a meticulous drug history, and also focus on signs and symptoms of tuberculosis or sarcoidosis. Travel, occupational history and risk factors for HIV infection are also of interest. A thorough clinical examination should include skin, eyes, lymph nodes and genitals. The assessment should be completed by HIV test, chest X-ray, serum calcium, angiotensin converting enzyme (ACE) and ANCA. At this point, the most likely diagnosis will be either drug-associated, sarcoidosis, tuberculosis or it will remain entirely unclear. Drug-induced cases are probably the most straightforward. If sarcoidosis appears likely then the next step should be to liaise with a respiratory physician to establish the diagnosis. In comparison, the situation is much more challenging if tuberculosis is suspected. Good dialogue with the renal

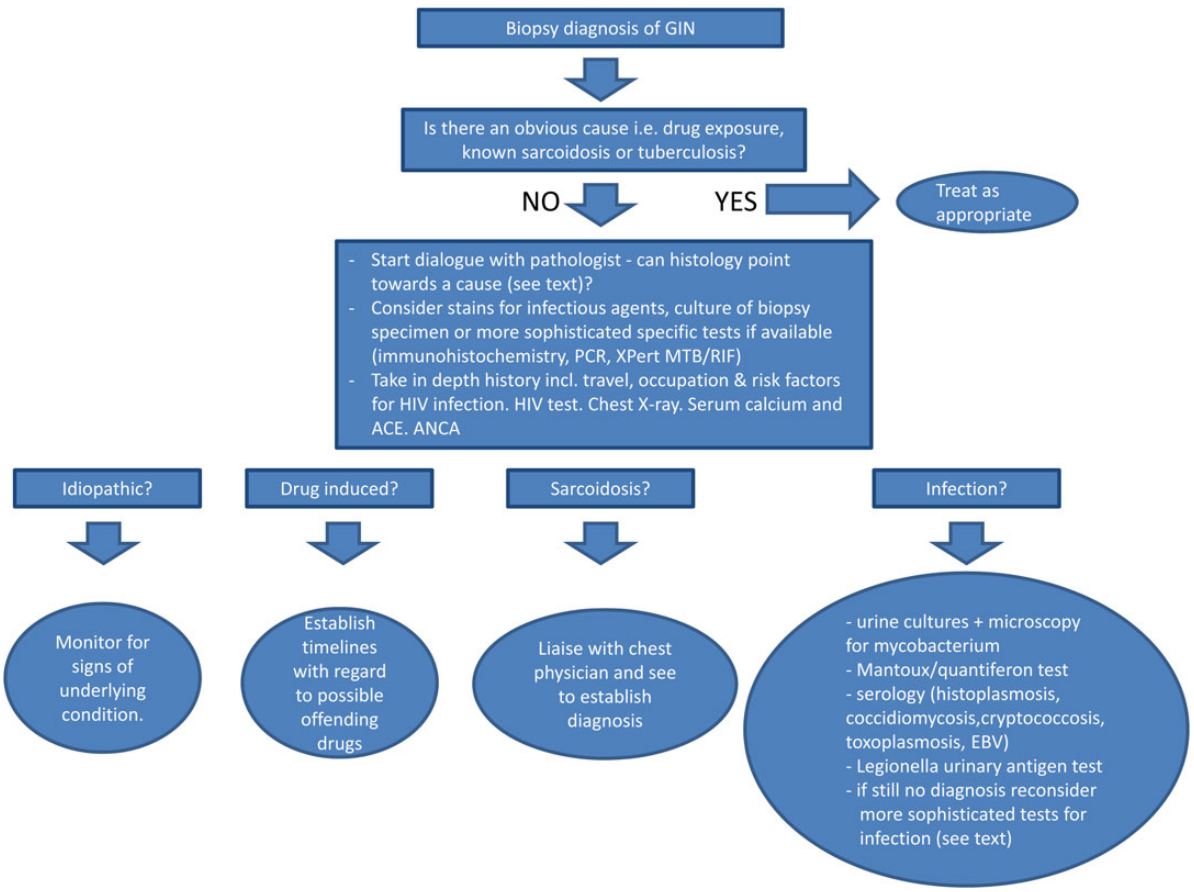


**Fig. 1.** Stepwise diagnostic approach to GIN. EBV, Epstein-Barr virus; LAM, lipoarabinomannan antigen.

pathologist needs to continue and further staining and testing should be guided by local availability and expertise. Another reason to be meticulous in this regard is the fact that a diagnosis of idiopathic GIN will usually mandate a trial of steroids—in the absence of anti-tuberculous therapy this is unlikely to be of any help if tuberculosis is the cause of GIN. A good example of this potentially lethal pitfall is a case described by Walker and co-workers who report a fatal case of disseminated histoplasmosis in a patient with GIN treated with steroids [29]. Histological features may be atypical, especially in patients who are immunocompromised, be it due to HIV infection or as a transplant patient or following chemotherapy. Culture of biopsy specimens is worthwhile, but results may take weeks [21]. It is therefore essential to initiate evaluation for bacterial, mycobacterial, fungal and viral infections as soon as possible to prevent any delay in definitive treatment and to look closely for evidence of tuberculosis elsewhere. More sophisticated tests, such as molecular testing for *Mycobacterium tuberculosis*, immunohistochemical techniques, enzyme-linked immunosorbent assay tests for mycobacterial antigens in serum or the urine should be used according to local availability or expertise. In this issue of *CKJ*, Agrawal *et al.* add that multiplex PCR for tubercular DNA is a useful and reliable diagnostic tool for supporting diagnosis of GIN due to tuberculosis [2], with some previous pessimistic results on PCR most probably being attributable to old specimens [13]. What to do if a case appears truly idiopathic? Going through the list of causes [1, 3] one last time would seem like a good idea, with consideration of re-testing if there is substantial evidence for one of the rarer causes. Vigilance is certainly warranted in that manifestations of underlying disease may well appear later on.

## Treatment

It is difficult to come up with any evidence-based recommendations for treatment of GIN, given that the disease is rare and also heterogenous. In drug-associated GIN, withdrawal of the offending drug may result in rapid recovery of renal function. However, most nephrologists advocate a trial of steroid treatment if GIN is felt to be drug-associated even if the offending drug has been stopped and without waiting for spontaneous recovery. Across all causes of GIN the renal prognosis appears to be favourable: in one of the largest series so far Joss and co-workers reported that only 1 out of 18 patients required dialysis, although most patients did not recover fully [1]. The outcome appears to be worse in GIN due to tuberculosis [3]. The treatment of renal sarcoidosis remains poorly defined but most authors will agree that GIN as a feature of sarcoidosis requires steroid treatment [30]. Doses between 0.5 and 1 mg/kg body weight are used and response to treatment is usually good although relapses are common. In patients with extra-renal manifestations dialogue with respiratory medicine is required to establish treatment. Therapeutic options for renal sarcoidosis are reviewed in detail elsewhere [30]. For patients with infection as underlying aetiology of GIN, treatment consists of specific antimicrobial therapy while the role of corticosteroids remains unclear. Interestingly, neither the British nor the American Thoracic Society guidelines [31] provide guidance for GIN due to tuberculosis. Some authors favour tuberculostatic therapy alone [19, 26], whereas others combine with steroid treatment [13]. Since granulomatous inflammation heals by fibrosis, concomitant use of steroids might reduce fibrosis. We suggest careful risk assessment before steroid treatment is considered in GIN associated with tuberculosis. Another difficult scenario may arise where a patient from an endemic region presents with GIN but tuberculosis tests remain negative or equivocal, or if the disease remains truly idiopathic. In light of the two articles in this issue of the journal perhaps one needs to consider at least tuberculostatic prophylaxis when embarking on steroid treatment in at risk patients, i.e. those from endemic regions or the immunosuppressed.

## Conclusion

GIN remains a chameleon and drugs, sarcoidosis and infections are the main causes. Drug-associated cases are common in Western countries whereas infection (mainly tuberculosis) prevails in tropical countries. In Jules Verne's *Around the World in 80 Days*, Phileas Phogg remarks that he could have shortened the trip (by a meagre 2 days) by not passing through India [32]. However, like Phogg we benefit from the experience from India, in this case the emphasis on infectious causes of GIN. And, like Phogg, who could not have done his travels without his talkative companion Mr Passepartout (literally translated 'goes anywhere'), we would be lost without our trusted renal pathologist with whom we can go anywhere and who invokes the explorer in us.

## Conflict of interest statement

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

(See related articles by Shah *et al.* Granulomatous interstitial nephritis. *Clin Kidney J* (2015) 8: 516–523 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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