Granulomatous interstitial nephritis and Crohn’s disease

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Abstract
Granulomatous interstitial nephritis has been observed in <1% of native renal biopsies. Here, we describe two patients with granulomatous interstitial nephritis in relation to Crohn’s disease. Circulating helper and cytotoxic T cells were highly activated, and both cell types predominated in the interstitial infiltrate, indicating a cellular autoimmune response. After immunosuppressive treatment, renal function either improved or stabilized in both patients. In conclusion, granulomatous interstitial nephritis is a genuine extraintestinal manifestation of Crohn’s disease, the treatment of which should include immunosuppressive agents.

Key words: calcineurin inhibitors, Crohn’s disease, granulomatous interstitial nephritis, inflammatory bowel disease, T cells

Background
Extraintestinal manifestations of inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis, probably reflect systemic inflammation, autoimmune susceptibility and/or drug-related toxicities [1]. Although these manifestations are prevalent, parenchymal renal disease as such is considered rare. However, renal biopsies from patients with IBD can reveal a wide spectrum of pathologies most commonly affecting the glomerular and tubulo-interstitial compartments [2].

Granulomatous interstitial nephritis in the absence of glomerulonephritis or vasculitis has been associated with various aetiologies, particularly with drug hypersensitivities, infections and miscellaneous causes such as sarcoidosis, while others are classified as idiopathic to conceal our ignorance about causes [3–5]. Ambrozus et al. [2] found granulomatous interstitial nephritis in ~5% of renal biopsies from patients with IBD, the occurrence of which was linked to current or recent past exposure to 5-aminosalicylic acid (5-ASA) preparations. Because of their study design, a causal relationship cannot be concluded, however. Here, we report two patients with granulomatous interstitial nephritis in relation to Crohn’s disease, which was not associated with 5-ASA. On the basis of our clinicopathologic observations, a pathophysiological mechanism has been proposed.

Case reports
Case 1
A 19-year-old man who had been well until 4 months previously presented with abdominal discomfort and changing bowel habits. Although his appetite was normal, he had lost 6 kg of weight.

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The review of systems was entirely negative. There was no history of ingestion of any drugs. On physical examination, no abnormalities were found. Laboratory tests showed mild normochromic normocytic anaemia and an increased CRP of 38 mg/L. The white blood cell count revealed no abnormalities. Serum creatinine was 177 µmol/L [estimated glomerular filtration rate (eGFR), 43 mL/min/1.73 m²], and isolated aseptic leukocyturia was present. A renal biopsy was obtained and revealed granulomatous interstitial nephritis. Chest X-ray and an interferon gamma release assay for tuberculosis were unremarkable. Also, endoscopic biopsies of the terminal ileum and colon were obtained because of the abdominal complaints and an increased faecal calprotectin of 1136 µg/g (reference range, <150 µg/g), after which a diagnosis of Crohn’s disease was made. Granulomatous interstitial nephritis was therefore considered an extraintestinal manifestation of Crohn’s disease. The patient had been treated with three pulses of methylprednisolone, followed by oral prednisolone 50 mg/day (tapered to 5 mg/day over a 3-month period) and tacrolimus (target level of 5–7 µg/L). Currently, the patient is doing well with no signs of active disease. Renal function improved (serum creatinine, 133 µmol/L; eGFR, 60 mL/min/1.73 m²), while Crohn’s disease remitted.

**Case 2**

Subsequently, a 22-year-old woman with a history of biopsy-proven Crohn’s disease had been treated with mesalamine, mercaptopurine and adalimumab. All drugs were stopped because of remitting disease, after which serum creatinine increased from 101 to 160 µmol/L (eGFR, 37 mL/min/1.73 m²) and isolated aseptic leukocyturia developed. A renal biopsy revealed tubulo-interstitial nephritis without granuloma. Despite high-dose corticosteroids and monthly pulses of 500 mg cyclophosphamide for 6 months, serum creatinine increased to 233 µmol/L (eGFR, 23 mL/min/1.73 m²). Therefore, the patient was referred to our hospital.

At the time of presentation, abdominal discomfort was not present and her defecation was normal. Fatigue was reported, however. On physical examination, no abnormalities were found. Laboratory tests showed mild normochromic normocytic anaemia and an increased CRP of 114 mg/L. The white blood cell count revealed no abnormalities. Aseptic leukocyturia had persisted. Because of refractory disease, another renal biopsy was obtained, which revealed granulomatous interstitial nephritis. Positron emission tomography–computed tomography scanning of the whole body was unremarkable, as was the further workup for drug hypersensitivities, infections and common variable immunodeficiency. Thus, granulomatous interstitial nephritis as an extraintestinal manifestation of Crohn’s disease was diagnosed. The patient was treated with three pulses of methylprednisolone followed by oral prednisolone 50 mg/day (tapered over a 3-month period), mycophenolate mofetil (MMF) 2000 mg/day and ciclosporin 200 mg/day. Although her renal function and inflammatory markers initially improved, chronic kidney disease stage 4 (eGFR, 28 mL/min/1.73 m²) developed.

**Clinicopathologic findings**

Light microscopy of the renal biopsies revealed a predominant lymphocytic cell infiltrate, occasional eosinophils and the formation of noncaseating granulomata in the tubulo-interstitial compartment (Figure 1A), whereas glomerular and vascular lesions were not found. Fungi, acid fast bacilli, crystals and polarized material were not observed. Routine immunofluorescence was negative.

In Case 2, immunohistochemistry was performed, which revealed an abundant CD3+ T cell infiltrate including both T helper (CD3+ CD4+) and cytotoxic T cells (CD3+ CD8+); histiocytes (CD3– CD4+) were also observed (Figure 1B–D). Few polytypic plasma cells (CD138+) but no B cells (CD20+) were found. The phenotype of circulating lymphocytes was assessed by fluorescence-activated cell sorting analysis, and although the distribution of lymphocyte subsets was normal, T-helper and cytotoxic T cells were highly activated as illustrated by an enhanced HLA-DR expression (8.4 and 20.3%, respectively). Furthermore, increased levels of the soluble interleukin 2 (IL-2) receptor (11 600 pg/mL; reference range, <3154 pg/mL) were found.

**Discussion**

Granulomatous interstitial nephritis is considered an uncommon pathological finding (<1% of native renal biopsies) that has been associated with various aetiologies, of which drug hypersensitivities and sarcoidosis encompass the majority of cases [4, 5]. An extensive workup was unremarkable, and, thus, granulomatous interstitial nephritis as a genuine extraintestinal manifestation of Crohn’s disease was diagnosed.

Renal and lower genitourinary involvement in IBD usually manifest as urinary calculi and fistulas, which has been observed in 10–15% of patients [6]. Although parenchymal renal disease in IBD has been described [2], granulomatous interstitial nephritis as such is considered extremely rare. To the best of our knowledge, only 12 patients (including 7 case reports; Table 1) have been described in the English literature [2, 7–13]. Remarkably, both our cases were diagnosed over the past year, suggesting that the incidence may have been underestimated. Because all patients presented with renal impairment with only subtle urinary abnormalities, it is advisable that renal function should be monitored in all patients with IBD and that a renal biopsy should be considered for those patients with a persistent increase in serum creatinine.

The pathogenesis remains poorly understood. Although drug-induced nephrotoxicity by 5-ASA has been considered an aetiological factor in tubulo-interstitial nephritis [2, 14], there is no clear relationship between the duration and dose and the development of renal disease. However, our first case describes the concurrent presentation of granulomatous interstitial nephritis and Crohn’s disease in a treatment-naive patient, whereas there was no recent past exposure to 5-ASA in our second case. Furthermore, half the reported cases were not linked to 5-ASA (Table 1) [7–9, 12], suggesting another pathophysiological mechanism.

The predominance of T-helper and cytotoxic T cells in the renal interstitium combined with the highly activated nature of these T cells in the peripheral circulation suggest a cellular (auto)immune response directed against an antigen in the renal interstitium. Therefore, we postulate that during an active episode of Crohn’s disease these T cells have been primed and activated against gastrointestinal antigens and simultaneously against components of the renal interstitium, presumably due to antigenic cross-reactivity. These reactive T cells induce the differentiation of effector T cells, such as cytotoxic T cells, mediating cytotoxicity. Of note, serum levels of the soluble IL-2 receptor, a marker of T-cell activation, paralleled disease activity (data not shown), indicating that the soluble IL-2 receptor may be a useful biomarker of the disease.

There is no standard of care for the management of granulomatous interstitial nephritis. Joss et al. observed that corticosteroid treatment was effective in most patients with granulomatous interstitial nephritis regardless of the underlying cause [4]. However, the treatment of patients with granulomatous interstitial
nephritis as an extraintestinal manifestation of IBD can be challenging (Table 1). Calcineurin inhibitors were therefore started. Furthermore, MMF was added in the second case because of its efficacy in refractory interstitial nephritis [15]. During follow-up, renal function improved or stabilized in both patients, suggesting that a more aggressive immunosuppressive regimen may be beneficial in the treatment of such patients.

Table 1. Reported cases of granulomatous interstitial nephritis in patients with IBD

| Age (years, gender) | 5-ASA | Creatinine, t₀ (µmol/L) | Treatment | Creatinine, tₓ (µmol/L) | Follow-up (years) |
|---------------------|-------|-------------------------|-----------|-------------------------|-------------------|
| Crohn’s disease     |       |                         |           |                         |                   |
| Archimandritis and Weetch [7] | 22, M | N ND                    | colectomy | ND                      | 4                 |
| Marcus et al. [8]   | 16, F | N 221                   | CS, 6-MP, anti-TNFα | 185                    | 1                 |
| Unal et al. [9]     | 43, M | N 229                   | CS        | 185                     | 0.1               |
| Polci et al. [10]   | 56, M | Y 274                   | CS, anti-TNFα | ESRD                   | 1                 |
| Colvin et al. [11]  | 23, M | Y 203                   | CS*       | 97                      | 1.8               |
| Saha et al. [12]    | 17, M | N 397                   | CS, AZA, anti-TNFα | 813                    | 1.5               |
| Timmermans et al.   | 19, M | N 177                   | CS, CsA    | 133                     | 1                 |
|                    | 22, F | N 233                   | CS, FK506, MMF | 186                    | 1                 |
| Ulcerative colitis  |       |                         |           |                         |                   |
| Alivanis et al. [13] | 19, M | Y 618                   | CS*       | 79                      | 1                 |

6-MP; 6-mercaptopurine; AZA, azathioprine; CS, corticosteroids; CsA, ciclosporine; ESRD, end-stage renal disease; FK506, tacrolimus; ND, not determined.

*cessation of 5-ASA after the diagnosis of granulomatous interstitial nephritis.

In conclusion, granulomatous interstitial nephritis is a genuine extraintestinal manifestation of Crohn’s disease, which is presumably due to systemic immune dysregulation and T-cell activation. Monitoring of renal function is therefore advisable regardless of 5-ASA treatment for patients with IBD. Furthermore, the use of additional immunosuppressive agents should be considered in addition to corticosteroids.
Authors' contributions
S.A.M.E.G.T., M.H.L.C., J.G.M.C.D., and P.v.P. have made substantial contributions to the conception and study design, acquisition of data and/or the analysis and interpretation of data. S.A.M.E.G.T., M.H.L.C. and P.v.P. drafted the manuscript. All authors revised the manuscript critically for important intellectual content and approved its final version for submission.

Conflict of interest statement
The results presented in this manuscript have not been published previously in whole or part, except in abstract format.

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