Seven cases of granulomatous interstitial nephritis in the absence of extrarenal sarcoid

Michael G. Robson, Debasish Banerjee, Debbie Hopster and Hugh S. Cairns

Abstract

Background. Renal disease in sarcoidosis may occur due to granulomatous interstitial nephritis. However, granulomatous interstitial nephritis in the absence of features of extrarenal sarcoid, or other causes, has been reported very rarely. In this report we describe seven such patients.

Methods. Since 1995, we have identified a number of patients with biopsy-proven granulomatous interstitial nephritis. Patients were excluded if they had (i) evidence of extrarenal sarcoid, (ii) infections that may have contributed to pathogenesis or (iii) an obvious drug-related aetiology.

Results. Seven patients were identified, of whom five were male and two female, with a median age of 69. Median calculated creatinine clearance at presentation was 14 ml/min. Two had raised serum calcium at presentation and three had a raised serum angiotensin-converting enzyme. All patients were treated with steroids and five out of seven had an improvement in their renal function. Two patients progressed to end-stage renal failure despite treatment with steroids.

Conclusions. Idiopathic granulomatous interstitial nephritis may represent a renal-limited form of sarcoid. It may be associated with hypercalcaemia and a raised serum angiotensin-converting enzyme and usually responds to treatment with corticosteroids.

Keywords: granuloma; interstitial; nephritis; renal; sarcoid; steroids

Methods

We identified patients seen in our clinic since 1995 with histological evidence of GIN on renal biopsy. Any patients with evidence of extrarenal sarcoid or an infectious cause for this renal lesion were excluded from the analysis, leaving a total of seven patients with idiopathic GIN. During this period we performed 950 native renal biopsies; therefore 0.74% had idiopathic GIN. The patients were analysed with respect to epidemiological and clinical features, including response to therapy with corticosteroids. Creatinine clearance was calculated from the formula:
Creatinine clearance = \left[ \frac{(140 - \text{age}) \times \text{weight(kg)}}{\text{serum creatinine(mg/dl)} \times 72} \right]

This was multiplied by 0.85 in women.

Results

A total of seven patients with a renal biopsy showing GIN in the absence of evidence of extrarenal sarcoid were identified. Five patients were male and two were female, with a median age of 69 years (range 35–72). Their histories and responses to steroid treatment are described below. The clinical presentation, initial calculated creatinine clearance, steroid treatment and response to treatment are summarized in Table 1. The typical histological appearances of a renal biopsy specimen are shown in Figures 1 and 2. Figure 1 is a low-power view of a renal biopsy showing normal glomeruli but marked chronic tubular atrophy and interstitial expansion by fibrosis and chronic inflammation. In addition, there are several granulomata, but these are seen best in Figure 2, which is a high-power view of a granuloma composed of epithelioid cells and a multinucleated giant cell. In none of our patients was there evidence of any glomerular disease. In addition, none of our patients had clinical or ultrasonographic evidence of nephrolithiasis or nephrocalcinosis.

Case 1

A 35-year-old Afrzo-Caribbean male was incidentally found to have renal impairment when seen with a pilonidal abscess. He had been taking no medication. There were no other remarkable clinical findings and blood pressure was normal. He was known to have had a calculated creatinine clearance of 27 ml/min (serum creatinine 400 μmol/l) 5 months previously. Calculated creatinine clearance at presentation was 21 ml/min (serum creatinine 512 μmol/l). Proteinuria was < 0.5 g per day. Serum calcium, serum angiotensin-converting enzyme (ACE) and chest X-ray were normal. Liver function tests showed a mildly elevated alkaline phosphatase of 206 IU/l, a raised aspartate aminotransferase (57 IU/l) and gamma glutamyltransferase (159 IU/l), with a normal bilirubin. Urine culture was negative.

Table 1. Clinical features of patients with renal-limited sarcoid

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Proteinuria (g/day)</th>
<th>Corrected calcium (mmol/l)</th>
<th>Serum ACE (normal 16–43 U/l)</th>
<th>Initial calculated creatinine clearance (ml/min)</th>
<th>Initial dose of prednisolone (mg)</th>
<th>Best calculated creatinine clearance (ml/min)</th>
<th>Outcome/latest calculated creatinine clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>M</td>
<td>&lt; 0.5</td>
<td>Normal</td>
<td>Normal</td>
<td>21</td>
<td>60</td>
<td>27 (2 months)</td>
<td>Dialysis (15 months)</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>0.772</td>
<td>3.47</td>
<td>195</td>
<td>10</td>
<td>30</td>
<td>20 (1 month)</td>
<td>21 (9 months)</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>&lt; 0.2</td>
<td>Normal</td>
<td>Normal</td>
<td>14</td>
<td>30</td>
<td>14 (initial)</td>
<td>Dialysis (3 months)</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>0.42</td>
<td>Normal</td>
<td>Normal</td>
<td>14</td>
<td>40</td>
<td>56 (2 months)</td>
<td>53 (48 months)</td>
</tr>
<tr>
<td>69</td>
<td>M</td>
<td>0.23</td>
<td>2.63</td>
<td>160</td>
<td>16</td>
<td>40</td>
<td>29 (3 months)</td>
<td>29 (3 months)</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>0.9</td>
<td>Normal</td>
<td>Normal</td>
<td>6 (dialysed)</td>
<td>40*</td>
<td>22 (56 months)</td>
<td>22 (56 months)</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>Minimal on urinalysis</td>
<td>Normal</td>
<td>55</td>
<td>29</td>
<td>20</td>
<td>44 (4 months)</td>
<td>31 (7 months)</td>
</tr>
</tbody>
</table>

*aFollowing intravenous methylprednisolone 500 mg × 3.

Fig. 1. A low-power view showing two normal glomeruli, extensive tubular atrophy and interstitial expansion by fibrosis and a chronic inflammatory cell infiltrate. Several granulomata are also seen (arrows). Haemotoxylin and eosin, magnification ×200.
for tuberculosis. Renal biopsy showed GIN with severe interstitial and periglomerular fibrosis. He was treated with prednisolone, originally at a dose of 60 mg a day. Although his calculated creatinine clearance initially improved to 27 ml/min (serum creatinine 411 µmol/l) at 2 months, his renal failure then progressed, partly related to poor compliance, and 15 months later he commenced renal replacement therapy.

Case 2
A 70-year-old Caucasian male presented with confusion, nausea and lethargy and was clinically hypovolaemic. There was no history of hypertension, although he was diabetic and had been taking gliclazide. He was on no other medication. Corrected calcium was 3.47 mmol/l, calculated creatinine clearance 10 ml/min (serum creatinine 435 µmol/l) and serum ACE was raised at 195 U/l. Chest X-ray was normal and proteinuria was 772 mg/day. Liver function tests were normal. His volume depletion and hypercalcaemia were treated with intravenous fluids, frusemide and bisphosphonates. His calculated creatinine clearance improved temporarily to 15 ml/min (serum creatinine 300 µmol/l), but then deteriorated to 10 ml/min (serum creatinine 435 µmol/l) and he underwent renal biopsy. This showed GIN. He was treated with prednisolone at 40 mg a day and 1 month later his calculated creatinine clearance had risen to 20 ml/min and his calcium was normal. At 9 months his calculated creatinine clearance was 21 ml/min (serum creatinine 213 µmol/l).

Case 3
A 66-year-old Caucasian female presented with unexplained renal impairment and a calculated creatinine clearance of 14 ml/min (serum creatinine 296 µmol/l). She had no systemic symptoms and no other significant symptoms or clinical findings. She had been hypertensive for 2 years, treated with enalapril and also took aspirin. She was known to have had an abnormal urea (11.2 mmol/l) 5 years previously, although creatinine was not measured. Renal ultrasound showed 9.4 and 9 cm kidneys with reduced cortical thickness and renal angiography was normal. The 24 h protein excretion was not raised and there was no haematuria. She had a renal biopsy which showed GIN. Chest X-ray, serum ACE and serum calcium were normal. Serum ACE may, however, have been lowered by the ACE inhibitor. Liver function tests showed a mildly elevated alkaline phosphatase of 128 IU/l, a raised GGT of IU/l, with a normal bilirubin. Enalapril was discontinued due to hyperkalaemia, but aspirin was continued. She was treated with prednisolone starting at 30 mg a day. Despite this, her renal function deteriorated and 3 months later she started renal replacement therapy.

Case 4
This 64-year-old Caucasian female presented with systemic symptoms including fevers and weight loss. She had long standing hypertension and had had dermatomyositis 20 years previously but had needed no treatment for 7 years. She had also had a duodenal carcinoid tumour. She was taking oxprenolol, lorazepam, zopiclone, ibuprofen and ciprofloxacin on admission. She was found to have advanced renal failure with a calculated creatinine of clearance of 14 ml/min (serum creatinine 436 µmol/l). Ibuprofen had been started at a time when her calculated creatinine clearance was already 20 ml/min (serum creatinine 300 µmol/l). She had 0.42 g/day of proteinuria. Chest X-ray, serum ACE and calcium were normal. Liver function tests were normal. She had a renal biopsy that showed GIN and was treated with prednisolone starting at 40 mg a day. Oxprenolol and lorazepam were continued, but the other medication she had been taking on
admission was stopped. Her calculated creatinine clearance improved rapidly; at 2 months it was 56 ml/min (serum creatinine 129 µmol/l) and has stayed at this level (53–56 ml/min, with serum creatinine 125–135 µmol/l) after 4 years of treatment.

Case 5
A 69-year-old Caucasian male was admitted with a 12 month history of lethargy and anorexia. He was seen with right upper quadrant pain and gall stones and incidentally found to have a calculated creatinine clearance of 16 ml/min (serum creatinine 493 µmol/l). He was known to have had a normal serum creatinine 1 year previously. Blood pressure was normal. He had been taking ibuprofen for back pain, although this was stopped 2 months prior to his renal biopsy. During this time there was continued deterioration in his renal function. Corrected calcium was 2.63 mmol/l, serum ACE was raised at 160 U/l. Renal biopsy showed GIN. He was treated with prednisolone starting at 40 mg a day and after 3 months his calculated creatinine clearance was 29 ml/min (serum creatinine 264 µmol/l).

Case 6
A 70-year-old Caucasian male presented with unexplained renal failure. He had a 3 week history of vomiting, anorexia and lethargy which was attributed to his uraemia. On admission he was taking atenolol, ibuprofen and omeprazole. Initial calculated creatinine clearance was 6 ml/min (serum creatinine 1243 µmol/l) and he required dialysis for several days. Chest X-ray, serum calcium and serum ACE were normal. Liver function tests were normal. He had 0.9 g/day of proteinuria. Renal ultrasound was normal and biopsy showed GIN. He was treated with prednisolone starting at 40 mg a day and after 3 months his calculated creatinine clearance was 29 ml/min (serum creatinine 264 µmol/l).

Case 7
A 72-year-old Caucasian male presented with unexplained renal impairment. There were no systemic symptoms or other remarkable clinical findings. He was known to have had a normal serum creatinine 18 months previously. His calculated creatinine clearance was 26 ml/min (serum creatinine 400 µmol/l) 4 months earlier when he had a transurethral resection of the prostate. He had no evidence of renal tract obstruction at this point. There was no haematuria and 24 h urinary protein excretion was normal. He was taking allopurinol, bumetanide and omeprazole at presentation. Calculated creatinine clearance was 29 ml/min (serum creatinine 357 µmol/l). Chest X-ray and calcium were normal, serum ACE was marginally raised at 55 U/l but calcium was normal. Liver function tests were normal. Ultrasound showed two normal-sized kidneys with no obstruction. He was not previously known to be hypertensive but required treatment for hypertension before renal biopsy. Renal biopsy showed GIN. He was given prednisolone starting at 20 mg a day and the medication he was taking at presentation was continued. At 4 months his calculated creatinine clearance had risen to 44 ml/min (serum creatinine 235 µmol/l) but fell at 7 months to 31 ml/min (serum creatinine 328 µmol/l).

Discussion
GIN is a well-described manifestation of sarcoidosis. The frequency with which GIN occurs in sarcoid has been estimated from post-mortem series and reports vary from 7 to 27% [7,8]. However, many of these cases may have been clinically silent and the frequency with which GIN causes clinically apparent renal impairment in unselected populations of patients with sarcoid is difficult to ascertain, as most reports are of selected populations from renal units. The largest series of patients with GIN includes 10 cases. Twelve additional patients without granuloma formation were included in this report although the absence of granulomas may represent an effect of sampling [10]. In addition, a single-centre study described the clinical features of six patients with sarcoid and GIN [9]. There are also numerous reports of one or two patients, many of which are summarized in Hannedouche et al. [9]. The patients referred to in these studies had evidence of granulomatous inflammation in both the kidney and at least one other organ. These studies suggest that the other clinical features of sarcoid do not differ in patients with GIN compared with the general population of patients with sarcoid and that GIN usually responds well to treatment with corticosteroids.

We have identified four reports of single cases of idiopathic GIN in the literature [11–14]. In these reports, there were no features of sarcoid in organs other than the kidney and there were no other causes of GIN apparent. Serum ACE was commented on in one of these cases and was normal. Serum calcium was commented on in two cases and was normal. In addition, a recent paper documents five cases of idiopathic GIN [15]. Only one had a raised serum ACE and serum calcium was normal in all cases. Our series of seven patients represents the largest series of idiopathic GIN reported. In contrast to the above series, we found a raised serum ACE in three out of seven patients and high corrected calcium in two of these cases. Two patients had mildly abnormal liver function tests, with liver function tests normal in the remainder. Chest X-ray was normal in all patients. We did not perform further
invasive tests, such as bronchoscopy, computerized tomography scan or salivary gland biopsies.

Before making a diagnosis of idiopathic GIN, it is important to consider other causes of GIN. GIN has been attributed to a variety of drugs, although proof that a particular drug is responsible is often circumstantial [16]. Supportive evidence may include a temporal relation between starting the drug and the development of renal failure or cessation of the drug and an improvement in renal function. In two patients (cases 1 and 3), abnormal renal function was noted at a time when no medication was taken. In none of the other cases was there a clear relation between starting a drug and the development of disease. However, it is impossible to exclude a drug-induced aetiology in these patients.

A variety of infections may also cause a granulomatous inflammation in organs including the kidney [17]. In all of our patients, staining of histological sections for mycobacteria and fungi were negative, as were urine cultures for tuberculosis. There was no evidence of any other infection that may have caused the granulomatous inflammation. The response to long-term steroid treatment in five of our seven patients is also against an infectious aetiology.

Interstitial nephritis associated with extrarenal sarcoid responds to treatment with corticosteroids. In a series of 22 patients with interstitial nephritis, of whom 10 also had renal granulomas, 61% of patients showed an improvement in renal function with steroid therapy [10]. A further observation in this report was that patients may show a relapse after withdrawal of steroids. This was seen in five patients and four improved on restarting steroid treatment. This suggests that long-term treatment with steroids may be necessary. Other reports confirm that GIN associated with sarcoid is steroid-sensitive. For example, all six patients reported in Hannedouche et al. [9] showed a response to steroids. However, serum creatinine does not generally return to normal, reflecting the irreversible renal damage commonly seen on biopsy. Even patients with severe chronic damage on renal biopsy may respond to steroids. For example, case 2 had 100% chronic tubular atrophy on biopsy but responded well to steroids. Although this suggests that even a chronically damaged kidney may respond to treatment, there may also be an element of sampling error in the biopsy obtained. Eight of the nine cases of renal-limited sarcoidosis referred to above were treated with steroids and seven showed an improvement in renal function, suggesting that renal-limited sarcoid responds in a similar manner to systemic sarcoid with renal involvement [11–15]. Our series of patients confirms that most patients with renal-limited sarcoid respond to steroids, although renal function does not usually return to normal. In five out of seven of our patients, serum creatinine fell in response to steroids, although the serum creatinine then returned to its previous level in one (case 7). As described above for GIN with extrarenal sarcoid, we have found that prolonged steroid treatment may be needed and we recommend continuing for at least 1 year. Two patients progressed to end-stage renal failure despite treatment, necessitating renal replacement therapy. However, one of these patients was known to have had advanced renal failure for several months prior to treatment and in addition may not have complied with treatment.

In conclusion, we have presented a series of seven patients with idiopathic GIN. None of the patients had evidence of sarcoid affecting other organs or another cause for GIN. Three had a raised serum ACE and/or hypercalcaemia, with five out of seven showing a response to steroid treatment.

References

7. Longcope WT, Frieman DG. A study of sarcoidosis based on combined investigations of 160 cases including 30 autopsies from Johns Hopkins Hospital and Massachusetts General Hospital. Medicine 1952; 31: 132–140