Isolated Renal Relapse of Sarcoidosis under Low-Dose Glucocorticoid Therapy

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Sarcoidosis is a multisystem disease of unknown etiology. Renal manifestation is rare and usually caused by hypercalcemia and nephrocalcinosis. Moreover, renal disease can occur as granulomatous interstitial nephritis (GIN), which is a histological diagnosis. We describe a case of sarcoidosis first presenting with multiple organ involvement including renal failure caused by severe GIN and subsequent remission on glucocorticoid therapy. After 18 months under low-dose prednisolone, the patient was readmitted with acute renal failure, histologically confirmed to be a relapse of renal sarcoidosis. Extrarenal manifestations of sarcoidosis were not present. Glucocorticoid dose was raised and kidney function again recovered significantly. Usual serologic markers of disease activity were not appropriate to indicate disease activity. Renal manifestation of sarcoidosis should be diagnosed by renal biopsy to guide therapy and probably requires larger glucocorticoid doses and prolonged treatment to prevent relapse.

KEY WORDS: glucocorticoid therapy; granulomatous interstitial nephritis (GIN); renal biopsy; sarcoidosis.

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INTRODUCTION

Sarcoidosis is a systemic disease of unknown cause presenting with protean features and heterogeneous organ manifestations. While the respiratory tract and the liver are predominantly affected, almost every organ can be involved. The course of illness may be self-limited or chronic with risk of relapse. Clinically relevant renal involvement of sarcoidosis is rare because most patients with renal manifestation remain asymptomatic. Typical renal complications are associated with hypercalcemia and hypercalciuria, resulting in nephrocalcinosis and nephrolithiasis.¹ Moreover, in sarcoidosis-related renal

disease, tubulointerstitial nephritis with formation of noncaseating granuloma; glomerular disease; obstructive nephropathy; and, rarely, end-stage renal disease can occur, emphasizing the importance of renal biopsy to guide therapy. Glucocorticoid therapy in sarcoidosis is effective and used to treat systemic disease including renal manifestation.² However, the appropriate intensity and duration of immunosuppressive treatment in sarcoidosis with renal involvement remains controversial. Part of the controversy is owed to the lack of indicators for progression and relapse.

CASE REPORT

A 51-year-old female was referred to the hospital because of unexplained elevation of serum creatinine and progressive shortness of breath. One month earlier, a chest radiograph had revealed diffuse interstitial pulmonary infiltrates. Antibiotic therapy had been started with ciprofloxacin assuming atypical pneumonia with concomitant urinary tract infection.

On admission, the obese patient was generally unwell and presented with dyspnoea, slightly red and injected eyes, but no edema or signs of left ventricular insufficiency. She reported morning cough, weakness, and some weight loss during the previous weeks. Laboratory findings revealed a serum creatinine level of 395 $\mu\text{mol/l}$ with an estimated glomerular filtration rate (eGFR) of 11 $\text{ml minute}^{-1} 1.73 \text{ m}^{-2}$. Serum C-reactive protein was markedly elevated (151 mg/l). Full blood count, electrolytes, and liver function tests were normal. Antinuclear antibodies, anti-DNA, and anticytoplasmic neutrophil antibodies were not detected and the complement system was not activated. Serology was negative for legionella, chlamydia, mycoplasma and cytomegaly, and influenza or parainfluenza, respectively, as was stain for tuberculosis. Proteinuria of 360 mg/day was detected but urinary sediment showed no dysmorphic erythrocytes. Immunofixation of urine and plasma were negative. Serum calcium concentration, urinary calcium excretion, 1, 25-dihydroxyvitamin D, and intact parathyroid hormone values were normal.

Thoracic computerized tomography (CT) scan confirmed bilaterally diffuse interstitial fine nodular infiltration. Also, several enlarged mediastinal lymph nodes, but not typical hilar lymphadenopathy, were observed. Diagnostic bronchoscopy was refused by the patient. Kidney morphology looked normal in ultrasound imaging. Because of progressive renal failure and clinical unresponsiveness to antibiotic and fluid therapy, renal biopsy was performed. The histological examination showed severe granulomatous interstitial nephri-

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tis (GIN) with prominent noncaseating epithelioid-cell granuloma typical of renal disease in sarcoidosis.

A diagnosis of stage III systemic sarcoidosis with multiple organ manifestations including kidneys, eyes, and lungs was confirmed. Additional laboratory tests revealed normal angiotensin converting enzyme (ACE) activity, but a 5-fold elevated level of soluble interleukin-2 receptor (IL-2R). Glucocorticoid therapy (60 mg prednisolone daily) was started, and subsequently, the patient recovered. Inflammation markers normalized after 2 weeks and serum creatinine decreased to $137 \mu\text{mol/l}$ with an eGFR of $38 \text{ ml minute}^{-1} 1.73 \text{ m}^{-2}$ within 4 weeks. The patient was discharged with stable kidney function and followed-up by her nephrologist. Prednisolone was tapered during the next few months, but unfortunately, the patient gained weight and developed glucocorticoid-induced diabetes mellitus, which was treated with repaglinide. In the absence of clinical signs of relapsing sarcoidosis, prednisolone was reduced to a maintenance dose of 5 mg every other day.

After 18 months since the first presentation, the patient was referred again to the hospital with a progressive increase of serum creatinine ($516 \mu\text{mol/l}$, eGFR $8 \text{ ml minute}^{-1} 1.73 \text{ m}^{-2}$) but normal diuresis. The low-dose prednisolone regimen was continued. The patient had no remarkable clinical symptoms. C-reactive protein was moderately increased (33 mg/l), the IL-2R level 1.5-fold elevated, and the ACE activity was again normal. Because of the patient's history of systemic sarcoidosis including the lungs, thoracic CT scan was repeated, showing an almost complete remission of pulmonary disease. Likewise, eye manifestations were not detected this time. Second renal biopsy, however, again revealed highly active severe GIN, which was even more pronounced than in the first

Figure 2. Course of IL-2R and creatinine levels and prednisolone dose.

histology (Fig. 1). Further evaluation of other organ involvement including liver function tests, parameters of calcium metabolism, pulmonary function, and electrocardiography yielded no pathological results.

In view of this histology, prednisolone dose was raised to 100 mg ($1 \text{ mg kg}^{-1} \text{ day}^{-1}$). During follow-up, inflammatory markers again normalized within 2 weeks and serum creatinine values continuously decreased to almost previous levels over the next 2 months (Fig. 2). Once kidney function had stabilized, glucocorticoids were tapered to the minimally effective dose controlling renal disease as monitored by creatinine level and eGFR. Additionally, dietary and lifestyle interventions were intensified to prevent worsening of diabetes.

DISCUSSION

The true incidence of renal disease in systemic sarcoidosis is unknown, but data from small nonrepresentative series of biopsy findings suggest that, in approximately 50% of all patients, some degree of morphological renal involvement can occur, supporting the importance of obtaining a renal biopsy to guide therapy.³ However, clinically significant renal disease is not common and is mostly caused by the disease-associated disorder in calcium homeostasis by pathologic overproduction of 1, 25-dihydroxyvitamin D. The excessive calcium absorption can lead to hypercalcemia and hypercalciuria, respectively, resulting in nephrocalcinosis or nephrolithiasis. Furthermore, polyuria often associated with hypercalcemia and hypercalciuria caused by antidiuretic hormone dysregulation can be complicated by hemodynamically mediated acute renal failure.^{1,4,5} In our case, all parameters of calcium metabolism were normal and urine output was not increased.

Typical interstitial nephritis with granuloma formation is a rare histological diagnosis made by renal biopsy. There are only small series and anecdotal reports of GIN in sarcoidosis available in the literature.^{6,7} Usually, GIN is not a disease of significant proteinuria and typically presents with minimal

Figure 1. Thoracic CT scan and renal biopsy (light microscopy, periodic acid-Schiff staining). A On first presentation, CT demonstrated diffuse interstitial fine nodular infiltrates of both lungs. Renal biopsy revealed severe epithelioid-cell granulomatous interstitial nephritis (GIN) with diffuse lymphocytic cellular infiltrates and granuloma. B Eighteen months later, CT showed an almost complete pulmonary remission. Rebiopsy revealed renal relapse presenting as highly active severe GIN with even more extent and confluent granuloma.

proteinuria and decreased kidney function.⁸ In this context, a variety of further different histological lesions associated with glomerular involvement in sarcoidosis including membranous nephropathy, diffuse proliferative or crescentic glomerulonephritis, and focal segmental glomerulosclerosis have been described in some cases and may emphasize the importance of renal biopsy to guide therapy.^{2,9,10}

The etiology of sarcoidosis has not yet been fully elucidated and different pathogenic and immunologic mechanisms have been discussed. Most likely, exposure to unknown organic or inorganic agents stimulates a local inflammation involving increased macrophage and CD4 helper T-cell activity leading to granuloma formation in various tissues.¹¹ Recent studies have suggested a prominent role for tumor necrosis alpha (TNF- α) in progressive sarcoidosis.¹² An infectious origin of the disease has also been postulated, with propionibacterium acnae being one of the favorites.¹³ However, an additional defect in controlling pulmonary inflammation, e.g., in response to inhaled agents, is discussed and single nucleotide polymorphisms have been recently discovered in support of this hypothesis.¹⁴ Finally, suppressed immune responses to antigens such as tuberculin may contribute by entertaining the coexisting anergic state.^{11,15}

Tools for monitoring and assessment of disease activity have long been a matter of dispute. Commonly used serologic markers such as hypercalcemia, C-reactive protein, ACE activity, and IL-2R are not always detectable or lack specificity for diagnosis and as predictor of disease progression and relapse.¹⁶ Alternative measures of macrophage activation such as neopterin or inflammatory cytokines (TNF- α) may be helpful but are, at this time, still without sufficient predictive value for clinical routine.

Prognosis of sarcoidosis is based on the stage of the disease at initial presentation. Typically, spontaneous recovery, progressive deterioration, or relapse can be observed. In 1 study, relapses were detected in 37% of patients with a clinical manifestation similar to that at initial presentation in the majority of cases.¹⁷ In contrast, in our case, the clinical course developed differently. The patient initially presented with systemic disease and multiple organ manifestations. Under gradual tapering to a minimal low-dose glucocorticoid therapy (prednisolone 5 mg/alternate-day), a large degree of remission in tissues involved at the patient's first presentation could be achieved and maintained for more than 1 year. Interestingly, despite continued immunosuppressive therapy, the patient developed a severe renal relapse of sarcoidosis without additional organ manifestation.

Glucocorticoid therapy is the treatment of choice for sarcoidosis and usually decreases inflammatory activity and hypercalcemia.¹¹ Alternatively, hydroxychloroquine and ketoconazole are useful therapeutic agents in the setting of abnormal calcium metabolism.¹⁸ Thus, in sarcoidosis presenting with GIN, steroid treatment is established. However, renal recovery is often incomplete because of the chronic nature of the disease, and irreversible renal damage remains.^{6,19,20} Also, if steroids are tapered too rapidly or withdrawn, relapse and progression of sarcoidosis can occur.^{7,11} In a recent series of 18 cases with GIN including 5 associated with sarcoidosis, the mean length of steroid treatment was 25 months (range 2 to 82). Four of the 6 cases relapsed after reducing the prednisolone dose had sarcoidosis as the underlying causative factor. All patients with GIN relapse responded to an increase in steroid dose and remained on prednisolone long-term. However, no patient of

this series had a second renal biopsy.⁸ In our case, low-dose prednisolone as applied for long-term therapy was probably sufficient to control the disease regarding pulmonary and eye involvement but not to prevent renal relapse.

Common treatment protocols suggest a starting glucocorticoid dose (e.g., prednisolone 0.5–1 mg kg⁻¹ day⁻¹) with gradual tapering to establish the minimal effective dose for maintaining remission.^{11,19,20} Even in patients with advanced renal disease, glucocorticoid therapy can induce remission and long-term maintenance treatment is effective to preserve kidney function and prevent progression to end-stage renal disease.²¹ Alternative therapeutic approaches with various steroid-sparing immunosuppressive agents including infliximab, an anti-TNF- α monoclonal antibody, are promising in steroid-dependant or refractory cases but require further investigation.²²

In conclusion, patients with sarcoidosis and concomitant renal disease should undergo renal biopsy to guide therapy. Renal manifestation of sarcoidosis probably requires a larger glucocorticoid dose and prolonged long-term treatment to prevent relapse.

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REFERENCES

1. Muther RS, McCarron DA, Bennett WM. Renal manifestation of sarcoidosis. *Arch Intern Med.* 1981;141:643–5.
2. Casella FJ, Allon M. The kidney in sarcoidosis. *J Am Soc Nephrol.* 1993;3:1555–62.
3. Bergner R, Hoffmann M, Waldherr R, Uppenkamp M. Frequency of kidney disease in chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2003;20:126–32.
4. Singer FR, Adams JS. Abnormal calcium homeostasis in sarcoidosis. *N Engl J Med.* 1986;315:755–7.
5. Stuart CA, Neelon FA, Lebovitz HE. Disordered control of thirst in hypothalamic-pituitary sarcoidosis. *N Engl J Med.* 1980;303:1078–82.
6. Hannedouche T, Grateau G, Noel LH, et al. Renal granulomatous sarcoidosis: report of six cases. *Nephrol Dial Transplant.* 1990;5:18–24.
7. Robson M, Banerjee D, Hopster D, Cairns HS. Seven cases of granulomatous interstitial nephritis in the absence of extra renal sarcoid. *Nephrol Dial Transplant.* 2003;18:280–4.
8. Joss N, Morris S, Young B, Geddes C. Granulomatous interstitial nephritis. *Clin J Am Soc Nephrol.* 2007;2:222–30.
9. Toda T, Kimoto S, Nishio Y, Ehara T, Sasaki S. Sarcoidosis with membranous nephropathy and granulomatous interstitial nephritis. *Intern Med.* 1999;38:882–6.
10. Van Uum SH, Cooreman MP, Assmann KJ, Wetzels JF. A 58-year-old man with sarcoidosis complicated by focal crescentic glomerulonephritis. *Nephrol Dial Transplant.* 1997;12:2703–7.
11. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med.* 1997;336:1224–34.
12. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol.* 2002;168:4620–7.
13. Ishige I, Usui Y, Takemura T. Quantitative PCR of mycobacterial and propionibacterial DNA in lymph nodes of Japanese patients with sarcoidosis. *Lancet.* 1999;354:120–3.

14. **Valentonyte R, Hampe J, Huse K, et al.** Sarcoidosis is associated with a truncating splice site mutation in BTNL2. *Nat Genet.* 2005;37:357–64.
15. **Kettritz R, Goebel U, Fiebeler A, Schneider W, Luft F.** The protean face of sarcoidosis revisited. *Nephrol Dial Transplant.* 2006;21:2690–4.
16. **Gottlieb JE, Israel HL, Steiner RM, Triolo J, Patrick H.** Outcome in sarcoidosis. The relationship of relapse to corticosteroid therapy. *Chest.* 1997;111:623–31.
17. **Rizzato G, Montemurro L, Colombo P.** The late follow-up of chronic sarcoid patients previously treated with corticosteroids. *Sarcoidosis Vasc Diffuse Lung Dis.* 1998;15:52–8.
18. **Sharma OP.** Hypercalcemia in granulomatous disorders: a clinical review. *Curr Opin Pulm Med.* 2000;6:442–7.
19. **O’Riordan E, Willert RP, Reeve R, et al.** Isolated sarcoid granulomatous interstitial nephritis: review of five cases at one center. *Clin Nephrol.* 2001;55:297–302.
20. **Brause M, Magnusson K, Degenhardt S, Helmchen U, Grabensee B.** Renal involvement in sarcoidosis—a report of 6 cases. *Clin Nephrol.* 2002;57:142–8.
21. **Rajakariar R, Sharples EJ, Raftery MJ, Sheaff M, Yaqoob MM.** Sarcoid tubulo-interstitial nephritis: Long-term outcome and response to corticosteroid therapy. *Kidney Int.* 2006;70:165–9.
22. **Thumfart J, Müller D, Rudolph B, Zimmering M, Querfeld U, Haffner D.** Isolated sarcoid granulomatous interstitial nephritis responding to infliximab therapy. *Am J Kidney Dis.* 2005;45:411–4.