Tubulointerstitial Nephritis due to Sarcoidosis: Clinical, Laboratory, and Histological Features and Outcome in a Cohort of 24 Patients

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ABSTRACT. Renal involvement is rare in systemic sarcoidosis. Among renal manifestations, tubulointerstitial nephritis (TIN) is the most commonly reported finding. We conducted the current study to investigate the clinical, laboratory, and histological features and to analyze the outcome of TIN due to sarcoidosis. We present a retrospective, single-center study of patients followed for sarcoidosis and presenting with TIN related to this systemic disease. Twenty-four patients were assessed (22 females/2 males). The mean age at diagnosis of TIN was 46.3 years. Extrarenal manifestations were dominated by thoracic involvement (95.8%), peripheral lymph nodes (54.2%), and skin lesions (33.3%). The mean proteinuria level was 0.68 g/24 h. Renal failure was diagnosed in 83.3% of cases with a median estimated glomerular filtration rate at 14.3 mL/min/1.73 m². Nine patients presented with hypercalcemia and 12 patients with hypercalciuria. Renal biopsy was performed in 58.3% of cases. Six of the 14 patients presented with noncaseating granulomatous interstitial nephritis and eight with interstitial nephritis without granuloma. Granulomatous infiltration of renal parenchyma was complicated by vasculitis in two cases. Corticosteroid therapy was used in all patients. On follow-up analysis, four patients progressed to end-stage renal disease (ESRD) after a mean duration at 45.5 months. In the remaining patients, kidney function statistically significantly improved after one month of treatment compared to the time when the diagnosis was initially established (P = 0.031). We found that the predictive factors of progression to ESRD were multiorgan involvement (P = 0.032), advanced fibrosis F3 (P = 0.0006), and extensive interstitial granulomas (P = 0.007) and these were independently correlated with ESRD. Corticosteroid therapy seems to be effective in sarcoid TIN, but some degree of persistent renal failure is possible which can be predicted from both histologic findings and initial response to steroid therapy.

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Introduction

Sarcoidosis is an idiopathic multisystem illness of granulomatous inflammation that is postulated to be an autoimmune response to either an infection, possibly caused by Mycobacterium species, or an unknown environmental agent.\(^1,2\) Any organ system may be involved, but most commonly pulmonary, skin, lymphatic, and ocular.\(^1\) Renal involvement is rare\(^1,3\) but can be severe by progressing to irreducible and end-stage renal disease (ESRD). It is most often due to disorders in calcium homeostasis. The parenchymal involvement is frequently tubulointerstitial nephritis (TIN), and glomerulopathies remain exceptional.\(^4,6\) Renal biopsy has a very significant role in the diagnosis of sarcoidosis, especially in the absence of other extrarenal signs.\(^7\)

Corticosteroid treatment is the cornerstone of therapy. Its efficacy has been demonstrated in advanced sarcoid TIN. Immunosuppressive therapy may be required in some cases.

Only a few studies have addressed the specific issues of renal sarcoidosis (RS). We present here a single-center series of TIN due to sarcoidosis. We conducted the current study to describe the clinical, laboratory, and histologic features at presentation and to assess prognostic and therapeutic challenges.

Methods

We conducted a retrospective single-center study of patients diagnosed with renal sarcoidosis in our Department of Nephrology between January 1978 and December 2015. Twenty-four patients met the following inclusion criteria: (1) confirmed sarcoidosis according to the statement of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders;\(^8\) (2) pathologic renal findings of TIN such as polyuria/nocturia, mild proteinuria, normoglycemic glucosuria, metabolic acidosis, hypokalemia, aseptic leukocyturia with or without histologic findings in renal biopsy consistent with sarcoidosis, i.e., granulomatous or nongranulomatous TIN; and (3) exclusion of other alternative diagnoses. Note that in the absence of renal biopsy histology, the diagnosis of TIN was based on clinical, radiological, and laboratory findings associated with proved granulomatous localizations in at least two significant organs other than kidney.

For all cases, history, medical examination, results of urine sediment examination, chest X-ray, ultrasonography of the abdomen, and laboratory tests were compiled. The laboratory workup included blood count, kidney and liver panels, electrolytes, 24-h total protein and calcium secretion in urine, and C-reactive protein levels. When available, we evaluated the serum angiotensin-converting enzyme (ACE) and β2 microglobulin levels, indicating disease activity in sarcoidosis.

Hypercalcemia was defined as a serum calcium level >2.6 mmol/L and hypercalciuria as urine calcium excretion >0.1 mmol/kg/day. Renal abnormalities were evaluated using the following parameters: serum creatinine level (µmol/L), proteinuria defined as >0.3 g/24 h, hematuria as >10\(^6\) red blood cells/mL, and leukocyturia as >10\(^4\) leukocytes/mL. The stages of chronic kidney disease (CKD) were classified according to the estimated glomerular filtration rate (eGFR) in mL/min/1.73 m\(^2\) calculated using the Modification of Diet in Renal Disease formula.

Renal biopsy specimens were examined in our Laboratory of Renal Pathology. For light microscopy, the sections were stained with hematoxylin-eosin, periodic acid–Schiff, and Masson trichrome. Interstitial fibrosis was scored based on the degree of lesion in the cortical sample as follows: 0%–5% = F0, 6%–25% = F1, 26%–50% = F2, and >50% = F3. Immunofluorescence studies were performed in sections with antiserum direct against IgG, IgM, IgA, C3, C4, C1q, and light \(\lambda\) chains.

The follow-up was studied during the specified observation period, and the outcome was assessed by clinical and laboratory (urine sediment, serum creatinine level, eGFR, calcemia) evaluation at one month, six months, one year, and at the end of follow-up. The
need and time of initiation of dialysis were specified.

**Statistical Analysis**

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software for Windows version 19.0 (SPSS Inc., Chicago, IL, USA). A descriptive analysis was used to study continuous variables (means, medians, standard deviations, and ranges) and the frequencies of categorical variables (N and percentages). Means were compared using the Student t-test or, when appropriate, Mann–Whitney nonparametric test. Percentages were compared with the Pearson’s Chi-squared test, or, when appropriate, the Fisher’s exact test. \( P < 0.05 \) was considered to denote statistical significance. Independent variables with \( P = 0.20 \) or less after univariate analysis were included in a multiple logistic regression model based on a stepwise ascending method.

**Results**

Twenty-four patients with TIN due to sarcoidosis were assessed. Twenty-two (91.7%) were women and two (8.3%) were men. The estimated prevalence of TIN due to sarcoidosis among all patients hospitalized in our department for sarcoidosis was 30.8%. The mean age at diagnosis of TIN was 46.3 ± 15.1 years (range: 18–69 years). There was no case of occupational or environmental exposure known to induce other granulomatous disease. The diagnosis of TIN occurred concomitantly with the diagnosis of sarcoidosis for 17 patients (70.8%) and occurred in the course of previously diagnosed sarcoidosis for the other seven patients (29.2%). Renal failure revealed sarcoidosis in 79.2% of cases (19 patients). The other circumstances of discovery were urine sediment abnormalities in 16.7% of cases (4 patients) and urolithiasis in 4.1% of cases (1 patient).

Twenty-three patients (95.8%) had thoracic involvement disclosed on chest X-ray (Table 1). Nineteen patients (79.1%) had restrictive pattern in pulmonary function tests. Bronchoalveolar lavage revealed lymphocytosis higher than 15% in 17 patients (70.8%), with a lymphocyte T CD4/CD8 ratio higher than 3.5 in 10 of 17 patients (58.8%). Extrathoracic localizations (renal excluded) are summarized in Table 1. Constitutional symptoms (fever >38°C, asthenia, and weight loss >3 kg) were present in 22 cases (91.6%). Eight patients

Table 1. Epidemiological and clinical features in patients with tubulointerstitial nephritis at presentation.

| Parameters                          | Number of patients (%) |
|-------------------------------------|------------------------|
| Mean age (years)                    | 46.3±15.1              |
| Female/male                         | 22/2 (91.7/8.3)        |
| Intrathoracic involvement           | 23 (95.8)              |
| Initial chest X-ray stage           |                        |
| Stage 0                             | 1 (4.2)                |
| Stage I                             | 10 (41.6)              |
| Stage II                            | 9 (37.5)               |
| Stage III                           | 3 (12.5)               |
| Stage IV                            | 1 (4.2)                |
| Extrathoracic localizations         |                        |
| Peripheral lymph nodes              | 13 (54.2)              |
| Skin                                | 8 (33.)                |
| Uveitis                             | 7 (29.2)               |
| Parotiditis                         | 4 (16.7)               |
| Neurosarcoidosis                    | 4 (16.7)               |
| Liver                               | 3 (12.5)               |
| Spleen                              | 2 (8.3)                |
| Cardiac                             | 1 (4.2)                |
| Multiorgan (>3) involvement         | 17 (70.8)              |
Presented with hypertension (33.3%), with a mean systolic blood pressure of 151.8 ± 10.6 mm Hg (range: 140–170) and a mean diastolic blood pressure of 91.3 ± 6.4 mm Hg (range: 90–110). Urine sediment analysis showed a moderate proteinuria (1+ to 2+) in 20 patients (83.3%), hematuria in eight (33.3%), glycosuria without hyperglycemia in nine (37.5%), and leukocyturia in five patients (20.8%) (Table 2).

Some signs of tubular dysfunction were noted as follows: metabolic acidosis in 45.8% of cases (11 patients), hypokalemia in 33.3% of cases (8 patients), and hypophosphatemia in 8.3% of cases (2 patients). The mean proteinuria level was 0.68 ± 0.26 g/24 h (range: 0.3–2). Renal failure was diagnosed at presentation in 83.3% of cases (20 patients). The median serum creatinine level was 313 µmol/L (range: 64–1732) and the median eGFR was 14.3 mL/min/1.73 m² (range: 2.3–126.5). The repartition of patients according to CKD stages is summarized in Table 2. The mean calcium level in the entire cohort was 2.5 ± 0.31 mmol/L (range: 1.85–3.27). Nine patients (37.5%) presented with hypercalcemia with a mean calcium level of 2.97 ± 0.2 mmol/L (range: 2.77–3.27). Hypercalciuria was noted in 12 patients (50%), and it was complicated by nephrolithiasis in eight cases and nephrocalcinosis in one case. Serum ACE was increased in 16 patients (66.7%) and β2 microglobulin was increased in three cases. Biologic inflammatory syndrome was noted in 18 cases (75%).

Fourteen patients (58.3%) underwent renal biopsy. For the other 10 patients, it was not performed because of decreased kidney diameter <9 cm in five cases and because of absence of indication in the five others (patients with clinical and biological features of TIN and at least two histologic evidence of sarcoidosis in organs other than kidney). Six of the 14 patients (42.8%) presented with non-caseating granulomatous interstitial nephritis (GIN) and eight (57.2%) with interstitial nephritis without granuloma. Interstitial giant cells were associated in nine cases (64.3%). Epithelioid granuloma and interstitial lesions are illustrated in Figure 1. Acute lesions were mainly governed by interstitial inflammatory mononuclear cells infiltrate (78.6%) and tubular necrosis (57.1%). Chronic lesions were presented by fibrosis (85.7%) and tubular atrophy (28.6%). Interstitial fibrosis was present to varying degrees (Figure 2). Glomeruli were normal for all cases except in one biopsy which showed glomerular thrombotic micro-

| Parameters                              | Number of patients (%) |
|-----------------------------------------|------------------------|
| Proteinuria                             | 20 (83.3)              |
| Hematuria                               | 8 (33.3)               |
| Leukocyturia                            | 5 (20.8)               |
| Glycosuria                              | 9 (37.5)               |
| Hypercalcemia                           | 9 (37.5)               |
| Hypercalciuria                          | 12 (50)                |
| Biologic inflammatory syndrome          | 18 (75)                |
| Renal failure                           | 20 (83.3)              |
| Median creatinine (µmol/L)              | 313                    |
| Median eGFR (mL/min/1.73 m²)            | 14.3                   |
| CKD stages                              |                         |
| CKD 1                                   | 1 (4.2)                |
| CKD 2                                   | 2 (8.3)                |
| CKD 3                                   | 4 (16.7)               |
| CKD 4                                   | 3 (12.5)               |
| CKD 5                                   | 14 (58.3)              |
| Elevated ACE                            | 16 (66.7)              |

eGFR: Estimated glomerular filtration rate, CKD: Chronic kidney disease, ACE: Angiotensin-converting enzyme.
angiopathy associated with diffuse GIN (Figure 3a). This patient had no hypertension, and immunological analyses did not show any abnormalities (including antinuclear antibodies, antineutrophil cytoplasmic antibodies, complement, and antiphospholipid antibodies). Arteries were normal in the majority of cases. In two biopsies, granulomatous inflammation was distributed around arterioles, focally replacing the vascular wall media with disruption of the elastic lamina (Figure 3b). Immunofluorescence showed no deposits in 10 cases, rare interstitial deposits of C3 in three cases, and IgM in one case.

All patients received oral prednisone at 0.5 mg/kg/day (10 patients) or 1 mg/kg/day (14 patients). Intravenous pulse of methylprednisolone was administrated in two cases at 1 g/day for three days (for the two cases with vasculitis). The initial dose of prednisone was applied for one to two weeks and was tapered over the upcoming weeks. The median dura-

Figure 1. Histological features of sarcoid TIN (Masson Trichrome): (a) Low-power view showing interstitial inflammation, fibrosis, and epithelioid granulomas (arrow), (b) Diffuse granulomas (arrows) concentrated around vessels, (c) There is granuloma adjacent to a normal glomerululi without involvement of Bowman capsule, (d) Multinucleated giant cells and infiltration by lymphocytes.

Figure 2. Distribution of patients according to fibrosis score in renal biopsy.
tion of treatment was 18 months (range: 6–72 months). The two patients with vasculitis received also treatment with cyclophosphamide (0.5 g/m² per month for 6 months). Five patients benefited of hemodialysis for severe renal function with signs of uremia (3 cases) and hyperkalemia (2 cases). On follow-up analysis, four patients have evolved to ESRD after a mean duration at 45.5 ± 19.3 months. For the other patients, kidney function significantly improved after one month of treatment compared to the time when the diagnosis was initially established, reflecting a significant decrease of median creatinine levels from 313 to 224 µmol/L ($P = 0.027$) and an increase in median eGFR from 14.3 to 31.7 mL/min/1.73 m² ($P = 0.031$). This improvement in renal function was still significant when comparing response at one month with response at six months, one year, and at the end of follow-up (Table 3). A significant response to therapy at the end of follow-up was found to be strongly correlated with the response at six months ($P < 0.001$).

While evaluating the predictive factors of progression to ESRD in TIN due to sarcoidosis, using multivariate analysis we found that multiorgan involvement (>3 organs), advanced fibrosis F3, and extensive interstitial granulomas were independently correlated with ESRD ($P = 0.032, 0.006$, and $0.007$, respectively).

**Discussion**

Sarcoidosis is a systemic disease characterized by granulomatous lesions in various organs, particularly the lung and mediastinum. Renal involvement is uncommon, and patients can present late in the course of the

| Table 3. Evolution of median eGFR from presentation to the end of follow-up and correlation with response. |
|--------------------------------------------------------|------------------------|----------------|
| At presentation | Median eGFR | $P$ |
| At 1 month | 31.7 | 0.031 |
| At 6 months | 40.1 | 0.006 |
| At 1 year | 51.1 | 0.027 |
| At the end of follow-up | 47.2 | 0.014 |

eGFR: Estimated glomerular filtration rate.
disease as reflected by significant deterioration of renal function and the presence of fibrosis and tubular atrophy in renal biopsy. In the current study, we present a cohort of 24 cases of sarcoid TIN with data on epidemiological, clinical, laboratory, and histological features, but as well as treatment, long-term outcome, and predictive factors of renal impairment.

The clinical phenotype of patients with RS did not differ significantly from that of patients without renal involvement according to the ACCESS study showing similar prevalence of thoracic and extrathoracic localizations. Despite the reports that sarcoidosis affects more commonly women, we also observed in the literature a male predominance as well in RS In our study, we found in discordance to the existing literature a female predominance in patients with TIN such as described with sarcoidosis. RS occurred in the course of previously diagnosed sarcoidosis in seven (29.2%) patients, with a median of seven months after the initial diagnosis of sarcoidosis (range: 4–72). For the other 17 (70.8%) patients, RS occurred concomitantly with at least one other localization of the disease, which facilitated the sarcoidosis diagnosis. Among these cases, renal failure revealed sarcoidosis in 19 patients.

Most of our patients with TIN suffered from multiorgan extra-RS. This highlights the importance of searching kidney involvement before progressing to irreversible renal failure. Hypercalcemia and hypercalciuria are the two most common abnormalities in laboratory investigations in patients with RS. Hypercalcemia has been reported in 10% to 30% of cases and can lead to several significant clinical problems including renal failure. Hypercalciuria is most frequently reported (30%–60%) often with an insidious onset because most patients remain normocalcemic. In the current study, the prevalence of hypercalcemia reached 37.5%. The first hypothesis to be considered for this high frequency of hypercalcemia in patients with RS is that granulomas in the kidney could be an important source of calcitriol. On the other hand, hypercalcemia is aggravated by sunlight, and seasonal variation with higher levels of calcium during spring and summer has been previously reported, and our country is known to be sunny.

The most common parenchymal involvement remains TIN with or without granulomas. GIN is the most typical histological lesion in renal biopsy seen in 15%–40% of patients biopsied, although it usually manifests as acute or chronic renal insufficiency. Hence, the frequency of GIN is probably underestimated because granulomas are focal lesions that can be missed in renal biopsy. In our series, granulomas were noted in 42.8% of cases and nongranulomatous TIN in 57.2% of cases. This population did not differ from other patients with GIN. No other cause of interstitial nephropathy has been found. A histologic particularity of our patients was that in two cases, kidney biopsy showed the unusual feature of vasculo-centric granulomatous inflammation centered around arterioles with focal transmural destruction of the vascular wall, consistent with vasculitis. GIN with vascular involvement is a rare pathologic entity, and it has been described before, affecting large vessels or small vessels with necrosis. This entity supports the process of small arteries vasculitis rarely reported, associated in one of our cases with a glomerular thrombotic microangiopathy, which has not been reported previously. This highlights the aggressive nature of this disease with severe renal impairment.

Prednisone is the established treatment in all forms of sarcoidosis. In previously published literature, corticosteroid appeared to have a positive impact on preventing the progression of advanced renal disease. Mahévas et al and Rajakariar et al have documented in larger cohorts the efficacy of prednisone in RS. Löffler et al have also demonstrated the outcome so far after therapy. In our study, we confirm previous findings that corticosteroid therapy improves renal function. Nevertheless, in the cohort of Mahévas et al, complete response to therapy after initial presentation (1 year) was strongly correlated with positive response at one month. According to our data,
we found that an early response to therapy at 1 month is also crucial in terms of long-term outcome, but response at six months was strongly correlated to better results in terms of renal function at the end of follow-up. Mahévas et al and Rajakariar et al further established the degree of fibrosis as a prognostic factor of renal impairment. Our data confirm this proposal and found also a significant correlation between multiorgan involvement and interstitial granulomas and renal function impairment.

**Conclusion**

Renal manifestations in sarcoidosis are uncommon and can lead to chronic kidney failure and ESRD. Sarcoid interstitial nephritis can present with already advanced renal disease or with normal or moderately impaired renal function. We strongly recommend to consider diagnosis in all patients with sarcoidosis even in cases where kidney function is still normal. Renal biopsy remains the gold standard in establishing the diagnosis. Corticosteroid therapy seems to be effective in improving renal function, but persistent renal failure is possible which can be predicted from both histologic findings and initial response to steroid therapy.

**Conflict of interest:** None declared.

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