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Renal Involvement in Sarcoidosis

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Abstract

Introduction: Sarcoidosis is a granulomatous systemic disease. Renal damage is rare but it can evolve to chronic renal failure (CRF). The aim of our work is to describe the clinical, paraclinical, histological and evolutionary profile of renal involvement during sarcoidosis and to identify the progression factors leading to CRF. **Materials and Methods:** This is a retrospective descriptive study from January 2009 to December 2022. We collected the medical records of patients with sarcoidosis and renal involvement. To study the progression factors leading to CRF we identified two groups of patients: the group with normal renal function and the group that developed CRF. **Results:** We included in our study 17 patients with renal sarcoidosis. Their mean age was 45 ± 14.7 years and the sex ratio was 0.4. Renal involvement is revealing of sarcoidosis in 76% of cases. Renal failure was diagnosed in 88% of patients. Proteinuria was positive in 76.5% of cases, leukocyturia in 59% of patients and hematuria in 41% of patients. Renal biopsy was performed in 15 patients showing tubulointerstitial nephropathy in all biopsies. Epithelioid and giganto-cellular granuloma without caseous necrosis was found in 46% of cases. Associated glomerular involvement such as segmental and focal hyalinosis was found in 2 patients. Corticosteroid therapy was initiated in 88% of patients for a median duration of 15 months. Normalization of renal function was achieved in 41% of patients, while 59%, *i.e.* 10 patients, retained a CRF, including 2 who were on dialysis. We showed a statistically significant relationship between the evolution towards CRF and the presence of interstitial fibrosis > 25%. **Conclusion:** Despite its rarity, renal involvement can be revealing of sarcoidosis, which can condition the prognosis and lead to CRF. Its detection allows an early diagnosis and treatment.

Keywords

Sarcoidosis, Renal Failure, Tubulointerstitial Nephritis, Granuloma, Corticoids

1. Introduction

Sarcoidosis or Besnier-Boeck-Shaumann disease (BBS) is a systemic granulomatosis of unknown etiology. It results from an exaggerated immune response to one or more antigens, possibly triggered by environmental factors in genetically predisposed individuals [1] [2]. It is characterized histologically by the presence of non-caseating granulomatous lesions in the affected organs [3].

Sarcoidosis is most often manifested by involvement of the lungs and thoracic lymph nodes, but it can affect other organs such as the heart, skin, eyes, kidney and nervous system.

Renal manifestations are highly polymorphic, both clinically and biologically, and often go unrecognized, complicating known sarcoidosis or revealing the disease [4]. Renal involvement is rare in sarcoidosis [5], but is a major condition in the prognosis as it can evolve into chronic renal failure (CRF) in the event of delayed diagnosis or treatment.

The objectives of our study are to describe the epidemiologic, clinic-biologic, histologic and therapeutic characteristics of patients with renal sarcoidosis, to specify their evolutionary profiles and to study the progression factors leading to CRF.

2. Materials and Methods

2.1. Data Collection

This is a retrospective, descriptive and monocentric study, conducted at the Nephrology Department of the Ibn Sina University Hospital in Rabat, over a period of 14 years, from January 2009 to December 2022.

We included in this study, patients with known sarcoidosis with renal involvement of the type of renal failure defined by a glomerular filtration rate < 60 ml/min/1.73m^2 and/or an active urine sediment and/or positive proteinuria, and patients with a renal biopsy revealing sarcoidosis during a renal disease workup.

We excluded patients with sarcoidosis whose renal involvement was secondary to another pathology (diabetic nephropathy, nephroangiosclerosis, etc.), and patients with another granulomatosis (tuberculosis, pauci-immune vasculitides, histoplasmosis and berylliosis).

We analyzed the records of the patients admitted to the nephrology department during the study period, we noted the age, the sex and the history of sarcoidosis.

We recorded clinical examination parameters on admission including blood pressure, temperature, weight, lower extremity edema, and 24-hour diuresis.

Biologically, we recorded creatinine levels (mg/L) with estimated glomerular filtration rate (GFR) in mL/min/1.73m^2 according to the Modification of diet in renal disease (MDRD) formula, 24-hour proteinuria, urine sediment, angiotensin-converting enzyme (ACE), blood calcium, white blood cell count, lymphocyte count, and C-reactive protein (CRP).

The different biological anomalies were defined according to the laboratory's

reference standards, as follows:

- A positive 24-hour proteinuria is defined as a value greater than 0.3 g/d.
- An active urine sediment is defined as leukocyturia greater than 10/field and/or hematuria greater than 10/field.
- An elevated ACE level is defined as a level greater than 100 IU/L.
- Hypercalcemia is defined as a calcium level greater than 100 mg/L.

We also noted the radiological data, especially the renal ultrasound, specifying the size of the kidneys, their differentiation and the existence of a urinary calculus.

Histologically, we collected the results of biopsies of the different organs, namely the kidney, salivary glands and adenopathies.

Regarding the treatment, we noted the therapeutic protocols by specifying the route of administration, the dosage and the duration of the treatment.

To determine the factors of progression to CRF, after treatment, we identified two groups of patients: the group with normal renal function (DFR ≥ 60 mL/min/1.73m^2) and the group that developed CRF (GFR < 60 mL/min/1.73m^2).

We compared the two groups of patients. The analysis included risk factors such as age and sex, history of sarcoidosis, multivisceral involvement, renal histology including the existence of a granuloma or associated glomerulopathy and the percentage of fibrosis, corticosteroid therapy with its modalities and total duration.

2.2. Statistical Study

Data entry and analysis are performed using SPSS 21 (Statistical Package for the Social Sciences) software.

Categorical variables were expressed as numbers and percentages, and quantitative variables were expressed either as means ± standard deviations or as medians with interquartile ranges.

Comparisons of proportions were made using Chi^2 and T student tests, and the study of factors associated with progression to CRF was performed using a binary logistic regression model in univariate and multivariate analysis. A p value ≤ 0.05 was considered statistically significant.

3. Results

Over a period of 14 years, 17 patients with renal involvement associated with sarcoidosis. The mean age was 45 ± 14.7 years with extremes ranging from 22 to 71 years, and a sex ratio of 0.4.

3.1. Data related to Renal Involvement

Clinical examination on admission revealed hypertension in 17% of patients and edema of the lower limbs in 17%. Two patients presented oligo-anuria, while the rest of the patients had preserved diuresis.

Renal involvement was revelatory of sarcoidosis in 76% of cases, while in 24% of cases it appeared on average 8 years after diagnosis of sarcoidosis.

The disease was mainly represented by renal failure in 88% of the patients with a median creatinine level of 29 [18 - 69] mg/l, proteinuria was positive in 76.5% of cases with a median rate of 0.7 [0.35 - 1.69] g/d, microscopic hematuria was observed in 41% of cases and 59% of patients had leukocyturia, without associated urinary tract infection. The renal profile at admission is summarized in Table 1.

Abdominal ultrasound was systematic in all patients, showing normal-sized and well-differentiated kidneys in 15 patients (88%), while 2 patients had chronic kidney disease. We noted the presence of non-obstructive renal lithiasis in 2 patients.

Renal biopsy was performed in 88% of the patients (n = 15), showing chronic tubulointerstitial nephropathy in all biopsies. Epithelioid and giganto-cellular granuloma without caseous necrosis was found in 46% of cases (n = 7). Tubulointerstitial fibrosis appeared in 80% of patients, estimated to be less than 50% in 66% of patients and more than 50% fibrosis in 34% of cases (Figures 1-4).

Associated glomerular involvement such as segmental and focal hyalinosis was found in 2 patients.

We performed Biopsy of other organs in 7 patients (41%), of which 2 patients had small kidneys that contraindicated renal biopsy, thus confirming the diagnosis of sarcoidosis, with:

- Salivary gland biopsy in 6 patients, showing granulomatous sialadenitis;
- Bronchial biopsy in 2 patients, showing epithelioid and giganto-cellular granulomatous inflammatory remodeling without caseous necrosis.

3.2. Sarcoidosis-Related Data

We noted the presence of general signs in 59% of cases with weight loss in 41% of patients and fever in 23% of cases.

Biologically, ACE was elevated in 12% of cases, hypercalcemia was found in 18% of patients, hyperleukocytosis, without associated infections, was found in 23.5% of patients in the study, while lymphopenia was observed in 29.4% of them. CRP was elevated in 64.7% of patients, with a median level of 14 mg/L [3.0 - 28.5] (Table 2).

We noted extra-renal involvement of sarcoidosis in 94% of cases, mainly

Table 1.Renal profile at admission.

Variables	n = 17
Creatinine [a] (mg/l)	29 [18 - 69]
Creatinine clearance[a] (ml/min/1.73m^2)	22 [6.8 - 37]
proteinuria[a] (g/24h)	0.7 [0.35 - 1.69]
Leukocyturia[a] (elts/mm^3)	16 [4 - 58]
Hematuria[a] (elts/mm^3)	5 [1 - 18]

[a]Expressed in median [quartilles].

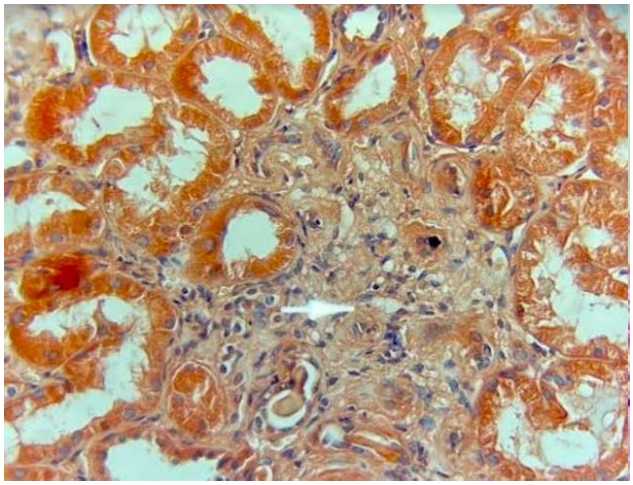

Figure 1. Sarcoidosis. Interstitial damage in the form of a focus of fibrosis (arrow) and tubular atrophy. Congo red staining

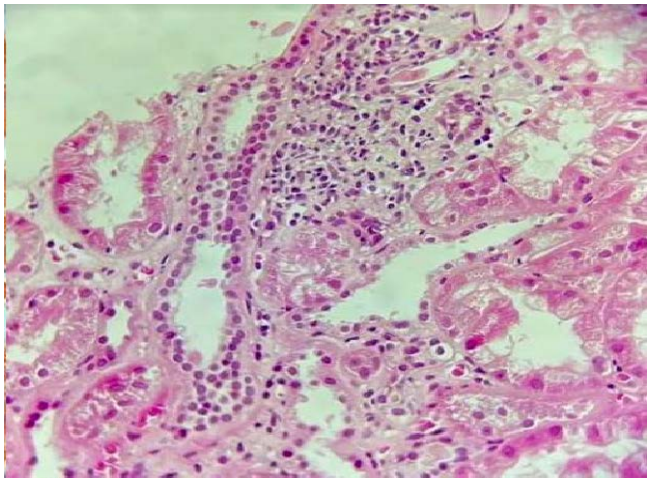

Figure 2. Sarcoidosis. Interstitial damage in the form of a focus of fibrosis (arrow) and tubular atrophy. Hematoxylin and eosin staining

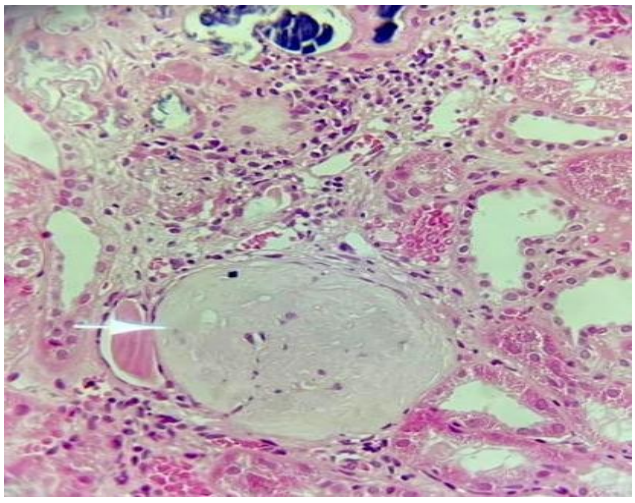

Figure 3. Sarcoidosis, sclerotic glomerulus (arrow), upper inflammatory interstitial focus with basophilic microcalcification. Hematoxylin and eosin staining.

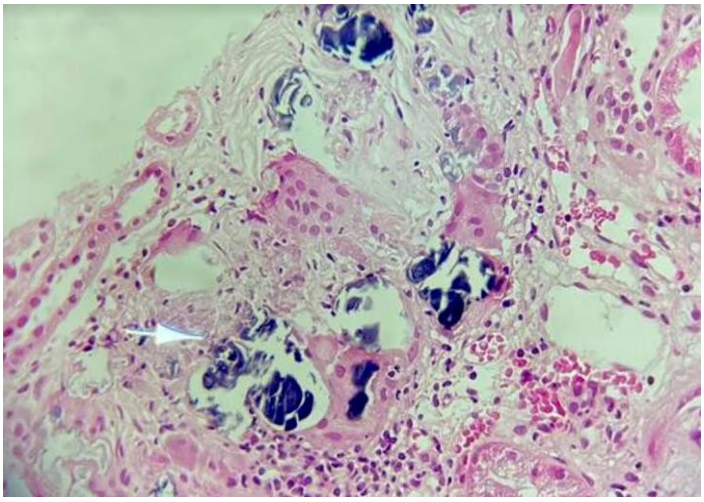

Figure 4. Sarcoidosis, interstitial basophilic microcalcification surrounded by an inflammatory foreign body-like giant cell reaction. Hematoxylin and eosin staining.

Table 2. Biological parameters at admission.

Variables	n = 17
ACE[a] (IU/l)	57 [37 - 102]
Calcemia[a] (mg/l)	91 [85 - 96]
GB[a] (elt/mm^3)	7020 [5370 - 10130]
PNN[a] (elt/mm^3)	5092 [3483 - 7795]
Lymphocytes[a] (elt/mm^3)	1050 [885 - 1500]
CRP[a] (mg/l)	14 [3.0 - 28.5]

[a]Expressed in median [quartilles].

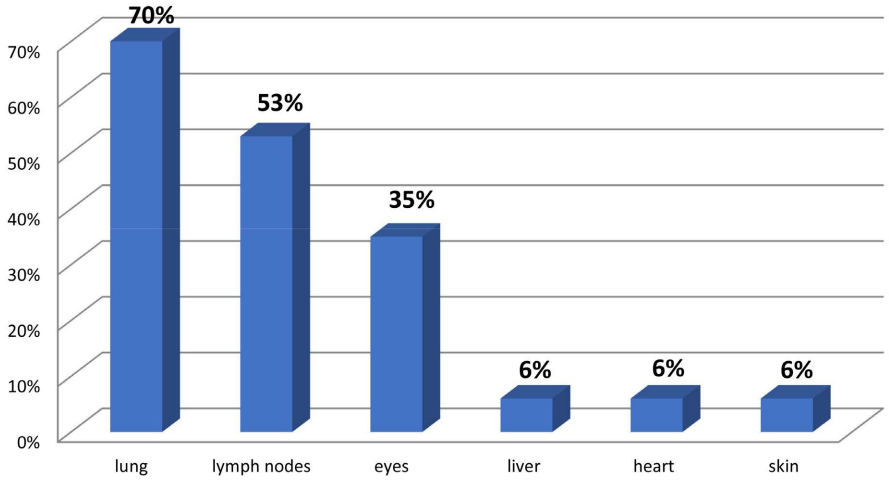

Figure 5. Extra-renal involvement in sarcoidosis.

pulmonary and lymph node involvement, Figure 5 illustrates the different extra-renal locations of sarcoidosis. Multivisceral involvement (≥3 organs) was noted in 53% of patients.

3.3. Therapeutically

Corticosteroid therapy was prescribed in 88% of patients (n = 15), in two modalities:

- A bolus of injectable methylprednisolone, 500 to 1000 mg/d for 3 days, followed by prednisone at a dose of 1 mg/kg/day in 47% of patients;
- Oral corticosteroid therapy alone with prednisone prescribed at a dose between 0.5 mg/kg/day and 1 mg/kg/day in 53% of cases.

The median decrease time of steroid therapy is 6 weeks with extremes ranging from 4 to 8 weeks. The median duration of steroid therapy is 15 months [8 - 24].

In our series, two patients did not receive treatment because the discovery of renal sarcoidosis was at the stage of advanced CRF without active extra-renal involvement.

The evolution is marked by:

- Normalization of renal function in 41% of our patients (n = 7)
- Progression to CRF in 59% of patients (n = 10):
  - CRF stage 3 in 29% of cases (n = 5)
  - CRF stage 4 in 18% (n = 3)
  - CRF stage 5 dialysis in 12% of cases (n = 2)

3.4. Statistical Analysis

We analyzed the risk factors for progression to CRF. In univariate analysis, we showed a statistically significant relationship with male sex (p = 0.041) and the presence of fibrosis > 25% on renal biopsy (p = 0.035). This association remained significant in multivariate analysis between the presence of fibrosis > 25% and progression to CRF (p = 0.033), with an odds ratio of 13.7 (Table 3 and Table 4).

Table 3. Predictive factors for progression to CRF in sarcoidosis in univariate analysis.

	Group A (n = 7)	Group B (n = 10)	P
Gender			
Male[a]	0	5 (29%)	0.041
Female[a]	7 (41%)	5 (29%)	
Age b (average in years)	44.3 ±13.8	45.4± 15.9	0.880
Unknown sarcoidosis[a]	5 (29%)	8 (47%)	0.559
HTA[a]	1 (6%)	2 (12%)	0.640
Creatinine clearance < 30 ml/min on admission[a]	5 (29%)	5 (29%)	0.354
Hypercalcemia[a] mg/l	0	3 (18%)	0.176
Multisystem damage[a] (≥3 organs)	3 (18%)	6 (35%)	0.419
Renal biopsy: (n = 15)			
Granuloma[a]	3 (18%)	4 (24%)	0.595
Fibrosis > 25%[a]	2 (12%)	7 (41%)	0.035

Continued

Corticosteroid therapy: (n = 15)			
Form of treatment: Injectable treatment[a]	4 (24%)	3 (18%)	0.268
Oral treatment alone[a]	5 (29%)	3 (18%)	
Average treatment time (months)[b]	17 ± 7.7	13.83 ± 7.55	0.490

[a]Expressed as a percentage; [b]Expressed as mean ± standard deviation.

Table 4. Factor analysis in mutlivariate analysis (binary logistic regression).

Factors	Odds ratio	Interval of trust	P value
Male gender	0.14	[0.02 - 1.16]	0.068
Fibrosis > 25%	13.7	[1.23 - 152.4]	0.033

4. Discussion

Sarcoidosis is a systemic disease, its pathophysiology remains poorly understood. It is considered to be the consequence of a chronic immunological response leading to granuloma formation, probably triggered by environmental factors in genetically predisposed individuals:

1) Genetics

Several studies have shown an association between sarcoidosis and certain HLA molecules, notably HLA-B8, and between favorable prognosis and the molecules HLA-DRB1*0301 and HLA-DQB1*0201 [6] [7].

Other susceptibility genes have been localized in certain regions of some chromosomes, mainly the 3p, 5q11.2, 6p and 6q regions. But their function remains to be established [8] [9].

2) Environmental Agents

Epidemiological studies have incriminated combustion products and insecticides in the occurrence of sarcoidosis, as well as exposure to humidity and pollens [10].

Infectious agents have also been suspected, including Mycobacterium tuberculosis and Propionibacterium acnes or granulosum [11] [12] [13] [14].

3) Immunity

The pathophysiology of sarcoidosis relies primarily on the CD4 T cell, whose interaction with the antigen-presenting cell is responsible for the formation of the granuloma [15]. The triggering pathogen promotes the accumulation and activation of specific T clones [16].

Our single-center study, conducted in the Nephrology Department, identified 17 cases of renal sarcoidosis. The average age of our patients was 45 years, but all age groups could be affected [17]. We observed a female predominance, which is in agreement with the data in literature where sarcoidosis usually predominates in women [18].

Renal involvement is an infrequent site of sarcoidosis, its prevalence varying between series depending on the diagnostic means used, and is between 10 and

20% [19]. A large cohort of 1200 cases of pulmonary sarcoidosis found that renal involvement was present in 12% of cases [20]. It has been shown in several studies that this involvement usually occurs in the context of multifocal sarcoidosis [17] [18] [20]. In our series, multifocal involvement (≥3 organs) was noted in 53% of cases.

Renal sarcoidosis can be revelatory of the disease as well as complicating a known sarcoidosis [21]. In our work, renal involvement revealed sarcoidosis in the majority of cases; 76% of cases, this result is similar to that of Mahévas where renal involvement was revealing of the disease in 81% of cases [18].

It is usually manifested by low-flow proteinuria < 1 g/d non-selective, leukocyturia and sometimes microscopic hematuria [5] [18]. In our series, proteinuria was positive in 76.5% of cases with a median rate of 0.7 g/d and a urine sediment abnormality was detected in 59% of patients.

Pathological study of renal biopsies reveals tubulointerstitial nephropathy in 74% - 85% of renal lesions in sarcoidosis [22] [23]. In our series, all renal biopsies performed showed tubulointerstitial nephropathy. The presence of epithelioid granulomas without caseous necrosis is more specific to sarcoidosis, but they are only found in 20% - 40% of cases, due to their focal distribution [24] [25] [26]. In our series, granuloma was found in 46% of cases. These data underline the interest of serial histological sections. Interstitial fibrosis was found in 80% of the biopsies, in line with the literature; interstitial fibrosis is important in sarcoidosis and may be present in up to 95% - 100% of cases to varying degrees [18] [22] [23], testifying to the profibrosing nature of this disease.

Glomerular nephropathy in sarcoidosis is rare and may coexist with interstitial nephropathy [27] [28]. It is mostly extramembranous glomerulonephritis [29] [30] [31].

Other renal lesions have been reported such as segmental and focal hyalinosis or membrano-proliferative glomerulonephritis [32] [33] [34]. The mechanism of glomerular damage in sarcoidosis is not known and is thought to be immunological in origin [35].

The reference treatment for sarcoidosis is corticosteroid therapy, the initial dosage being 0.5 to 1 mg/kg per 24 hours of Prednisone/Prednisolone [36] [37]. In cases of severe threatening sarcoidosis (severe optic neuritis or uveitis, renal involvement, cardiac involvement, neurological involvement, or laryngeal involvement), a dose of 1 mg/kg per 24 hours is preferred to optimize a rapid therapeutic response. A dose of 0.5 mg/kg per 24 hours can be proposed to reduce the risk of side effects, but with less success [19] [23]. Corticosteroid therapy should be initiated early to avoid the development of fibrosis. Oral treatment can be preceded by 3 boluses of methylprednisolone 500 to 1000 mg/d [37]. The Corticoidosis Study evaluated the efficacy of bolus methylprednisolone in improving renal function in patients with renal sarcoidosis, finding no benefit compared to oral corticosteroid therapy alone [38].

The duration of treatment is not codified but most teams recommend prolonged corticosteroid therapy with a minimum duration of 18 months [23]. In

our work, the median duration of treatment was 15 months. The suggested protocol for renal involvement in sarcoidosis is oral prednisone at a dose of 1mg/kg/d for 6 to 12 weeks, followed by a slow taper thereafter to a maintenance dose of 10 to 20 mg for 6 to 9 months [18].

Immunosuppressive drugs can be proposed in corticoresistant forms, including azathioprine [39].

During associated glomerulopathy, corticosteroid therapy alone is usually initiated [27] [40], immunosuppressants (azathioprine, cyclophosphamide) are exceptionally prescribed and the results are poorly evaluated.

In Mahevas' series, 76% of patients responded to corticosteroid therapy [18], compared to 59% in our series. In case of diagnostic and therapeutic delay with progression to fibrosis, corticosteroid therapy may be ineffective.

Factors influencing the progression to CRF during sarcoidosis are rarely evaluated [18] [23]. These include rare findings of poor renal prognosis in patients with multifocal involvement of sarcoidosis, the presence of significant interstitial fibrosis, and the presence of granuloma that promote the development of fibrotic lesions rapidly [18] [23].

In our study, we found a significant association between progression to CRF and the existence of >25% fibrosis on renal biopsy.

Our work had limitations related essentially to the monocentric nature of the study for an infrequent disease, the retrospective nature of the data collection and the change over time of the treatment protocol in our department.

5. Conclusions

Despite its rarity, renal involvement can be a revelation of sarcoidosis and can condition the prognosis and lead to CRF. It is a sign of severe disease, most often multi-visceral.

It is most often manifested as tubulointerstitial nephropathy; the absence of a granuloma lesion does not eliminate the diagnosis.

Treatment is based on prolonged corticosteroid therapy, which must be introduced early to prevent aggravation of the histological lesions that determine the response to treatment, in order to avoid progression to CRF.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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