SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 306-315

Renal Sarcoidosis: epidemiological and follow-up data in a cohort of 27 patients

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Abstract. *Background:* Renal sarcoidosis (RS) is a possible manifestation of systemic sarcoidosis. The clinical presentation can range from asymptomatic individuals up to acute renal failure with the necessity of renal replacement therapy. The definite diagnosis must be established by renal biopsy. *Objectives:* Demonstration of clinical characteristics and effectiveness of steroid treatment. *Methods:* We present a single center study of 27 patients with histologically proven RS. Firstly, we elaborate on descriptive features such as extra-renal organ involvement, calcium levels, renal function, proteinuria and histological subtypes and provide an histological assessment of renal damage. Secondly, we present follow-up data over a period of 2 years or more. *Results:* Non-granulomatous tubulointerstitial nephritis (ngIN) was the most common histological entity (44%), followed by granulomatous IN (GIN, 30%), IgA-GN (26%) and nephrocalcinosis (11%). Under treatment with oral prednisone mean eGFR significantly improved from 38 ± 21 ml/min to 57 ± 26 ml/min and proteinuria decreased from 981 ± 304 mg/24 hrs to 176 ± 77 mg/24 hrs at the end of follow-up. In total, 62.5% of patients responded to therapy. *Conclusions:* We demonstrated that GIN is more often associated with advanced stages of renal insufficiency than any other histological manifestation of RS. Furthermore, prednisone therapy is effective in improving eGFR and in reducing total urinary protein secretion. We suggest that the key prognostic factor for renal survival in RS is the early response to treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 306-315)*

Key words: histology, kidney, prednisone, renal, sarcoidosis, therapy

Introduction

Sarcoidosis is a multi-system autoimmune disorder with a heterogeneous clinical presentation most commonly affecting the respiratory tract. The typical histologic findings are T-lymphocyte infiltration, non-caseating epitheloid granulomas, and the destruction of normal cellular microarchitecture. Despite the fact that the process of granuloma formation is nowadays well understood (11) the factors triggering the disease cause have not yet been identified (24). The familial accumulation of sarcoidosis has led to the assumption of a genetic susceptibility and to the identification of several risk genes although the evidence for a convincing causative genetic pathomechanism is still lacking (9, 8).

As to the frequency of kidney involvement one can find various figures ranging from 3-48% (4, 14, 15, 17) possibly suggesting that renal involvement might be underdiagnosed. The mechanisms of kid-

Received: 9 Jenuary 204
Accepted after revision: 24 Apri 2014
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ney injury are diverse encompassing granulomatous and non-granulomatous tubulo-interstitial nephritis, nephrocalcinosis, glomerular involvement or even mimicry of a renal mass (1, 3, 4, 13, 18, 19, 21, 26). The clinical presentation can be as acute renal failure with the necessity of renal replacement therapy or as chronic kidney function impairment whereas the acute presentation seems to be more frequent (4, 12, 18, 20). Many authors have been suggesting the presence of renal involvement of sarcoidosis despite normal kidney function assessed by measurement of serum creatinine levels (8, 16, 17, 18). Renal biopsy is the gold standard in diagnosing renal sarcoidosis and is warranted when the suspicion of kidney involvement is given (23).

The backbone of treatment of renal sarcoidosis (RS) is the use of corticosteroids, the efficacy of which in preserving and improving kidney function has been suggested by previous authors (18, 21). Only very few patients remain dialysis-dependent. It has been postulated that kidney function after the first month of therapy is the key prognostic factor regarding the overall response to therapy (12).

By our retrospective study we want to add to the moderate pool of data there is on RS by presenting a cohort of 27 patients with biopsy proven RS, demonstrating clinical, laboratory, and histological findings as well as follow-up data.

Subjects and Methods

We conducted a single center retrospective analysis of 33 patients diagnosed with RS in our department of rheumatology and nephrology between the years 2000 and 2013. 27 patients met the inclusion criteria of (1) pathologic renal findings such as elevated serum creatinine levels (> 1.3 mg/dl; > 114.4 μmol/l), and/or elevated 24 hour total protein secretion in urine (> 120 mg/24 hrs, TPiU); (2) histologic findings in renal biopsy consistent with sarcoidosis, i.e. granulomatous or non-granulomatous tubulo-interstitial nephritis, glomerular disease, nephrocalcinosis, or combinations of more than one feature; (3) exclusion of alternative diagnoses.

From all patients we obtained a thorough medical history, physical examination, urine sediment, 24 hour proteine levels (TPiU), ultrasonography of the abdomen, and complete laboratory workup including blood count, kidney and liver panels, electrolytes, and c-reactive proteine (CRP)-levels. When available we evaluated the parameters indicating disease activity in sarcoidosis consisting of serum angiotensin converting enzyme (ACE), soluble interleukin-2 receptor (sIL2-R) and neopterin.

All patients not previously diagnosed with (non-renal) sarcoidosis were completely screened for extra-renal organ involvement using chest X-ray and/or computed tomography of the chest and/or the abdomen. In case of suspected pulmonary involvement spirometry and bronchoscopy were performed (data not shown). Mycobacterial infection was excluded with an enzyme-linked immunospot assay (TbElispot) and with cultures taken from bronchial lavage in patients that required bronchoscopy.

Hypercalcemia was defined as a serum calcium level > 2.6 mmol/l.

The stage of kidney disease was classified according to Kidney Disease Improving Global Outcomes (KDIGO) classification of 2012. The estimated glomerular filtration rate (eGFR in ml/min/1.73 m^2) was calculated by use of the CKD-EPI formula.

In our analysis only patients who underwent kidney biopsy before initiation of immunosuppressive therapy were included. Renal biopsy specimens were investigated by the Institute of Clinical Pathology and Cytology, Prof. Waldherr and Prof. Gross-Weissmann, Heidelberg, Germany, using light microscopy. The material was stained for hematoxylin-eosin and periodic acid-Schiff, and underwent an standard immunohistochemical staining for IgA, IgG, IgM, C1q, C3c, fibrin/fibrinogen and albumin.

In order to assess the degree of kidney damage renal histology findings were semi-quantitatively scored as to the degree of inflammatory activity (0 = none, 1 = focal, 2 = neither 0, 1 nor 3, 3 = extensive), tubular atrophy (0 = none, 1 = less than 33%, 2 = 33-66%, 3 = more than 66%) and degree of fibrosis (0 = none, 1 = focal, 2 = moderate, 3 = extensive).

In patients with interstitial nephritis we paid special attention to the patient's previous medication to exclude drug induced interstitial kidney damage. When not provideable by the patient we contacted the according general practitioner to be informed on the patient's medication.

Follow-up was either performed by our rheumatology clinic or by the patient's general prac-

titioner. In the latter case, we contacted the general practitioner to obtain follow-up laboratory kidney function tests in order to calculate changes in eGFR and TPiU (eGFR, TPiU) as retrievable. There was no standardized systematic follow-up regimen for the patients. For means of comparison we defined 4 points in time where data from kidney function and TPiU were assessed: t0 = time of diagnosis, t1 = 6-12 weeks after diagnosis, t2 = 40-70 weeks after diagnosis, t3 = 112 and more weeks after diagnosis.

Three patients were either lost to follow-up or had been newly diagnosed with RS with no data available apart from that of the initial diagnosis and hence were excluded form the follow-up analysis.

Statistical analyses were performed with SPSS for Windows version 11.5 and included variance analyses and t-tests. The level of significance was defined as 5%. Missing data in the follow-up data set were compensated for using the *last observation carried forward* (LOCF) method. In patients with impaired renal function before initiation of therapy (CKD 2 or higher) response to treatment was defined as either complete when improvement of eGFR was 50% or more to baseline, or partial when eGFR increased by 25-49% to baseline level. Patients with any change in eGFR less than 25% or showing a decline in eGFR were considered non-responders. In patients with initially normal creatinine based kidney function (CKD 1) response was defined as reduction of TPiU of 50% or more (complete response), respectively 25-49% to baseline (partial response). Any reduction in TPiU of less than 25% or an increment in protein secretion was considered treatment failure.

Results

Initially we evaluated thirty-three patients. Two patients with tubulo-interstitial nephritis were excluded because they were diagnosed with TINU syndrome (tubulo-interstitial nephritis and uveitis syndrome) and, therefore, had no definitive evidence of sarcoidosis as the underlying cause of the renal disease. Three more cases were discarded as they either lacked the necessary histologic features, or the clinical and/or laboratory data were insufficient for further analyses.

Epidemiologic, clinical and laboratory findings

The remaining twenty-seven patients showed a male to female ratio of 1.7 : 1. The mean age at diagnosis of RS was 55 years (range 25-86 years). Male and female patients were of the same age at diagnosis of RS (males 55 years, females 54 years).

The mean creatinine levels at baseline were 1.86 ± 1.5 mg/dl, the corresponding mean eGFR estimated by the CKD-EPI equation was 58 ± 34 ml/min. Eight patients (30%) had normal kidney function at the time of diagnosis whereas the 19 patients with impaired eGFR 78% were staged CKD 3 and higher reflecting an eGFR of 30 ml/min or less (table 1). In our cohort no patient required renal replacement therapy at any given time.

Mean total protein in urine (TPiU) was noted to be 1111 ± 1108 mg/24 hrs. None of the patients presented with nephrotic syndrome, i.e. the coexistence of proteinuria > 3g/24 hrs, edema, hypoalbuminemia, and dyslipoproteinemia. Sixteen patients (59%) presented with a pathological urine sediment, most notably microhematuria and leukocyturia. The presence of hyaline casts was rarely observed, cellular casts such as leukocyte or erythrocyte casts were not detected at all (table 1). Correlation analyses between the degree of TPiU and type of histology were not significant.

All patients received an ultrasound of the kidneys, however, in only two patients we found ultrasonographic evidence of chronic renal damage in form of decreased longitudinal kidney diameter and narrowed parenchymal layers. To ascertain alternative factors with a possible influence on renal health, e.g. other commonly occurring diseases such as hypertension and diabetes, we obtained a thorough past medical history. In 10 (37%) of our patients arterial hypertension and in seven (26%) a moderate diabetes mellitus type 2 was preexistent. In all cases these underlying diseases were well controlled and preexisting kidney function impairment or microalbuminuria respectively proteinuria was not known.

Six patients (22%) presented with hypercalcemia, in three of which it was clinically symptomatic and initially encouraged patients to present themselves to a health care institution. The mean calcium levels in the entire cohort were 2.47 ± 0.39 mmol/l.

In the vast majority of our patients RS occurred in concert with other organ manifestations of sarcoidosis.

We identified only 4 cases (15%) of isolated RS. The leading extra-renal manifestation was pulmonary (91% of all non-renal manifestations), foremost types 1 and 2. Cutanous lesions and extra-thoracic lymphadenopathy were the second leading incarnations of the disease, followed by granulomatous hepatitis. Other conditions such as CNS, gastrointestinal and peritoneal involvement have to be considered rare according to our data as elaborated in table 1.

Table 1. Clinical and laboratory features

	No. of patients	%
GFR		
normal (CKD stage 1)	8	30
impaired	19	70
CKD stage 2	5	26
CKD stage 3	7	37
CKD stage 4	3	16
CKD stage 5	4	21
dialysis necessary	0	0
Urine sediment		
normal	11	41
pathological	16	59
erythrocyturia	14	88
leukocyturia	10	63
hyalinated casts	2	13
Hypercalcemia	5	19
Isolated renal sarcoidosis	4	15
Extra-renal manifestations	23	85
pulmonary (total)	21	91
pulmonary type 0	1	4
pulmonary type 1	8	35
pulmonary type 2	7	30
pulmonary type 3	4	17
pulmonary type 4	1	4
cutanous	4	17
extra-thoracic LA	4	17
hepatic	3	13
ophthalmologic	2	9
CNS	2	9
GI-tract	1	4
peritoneum	1	4
ACE elevated	10	48 (tot. 21)
sIL2-R elevated	7	100 (tot. 7)
Neopterin elevated	5	83 (tot. 6)

Serologic parameters reflecting disease activity such as ACE, sIL2-R and neopterin were only infrequently tested in our cohort. Serum ACE was determined in 21 cases and turned out be positive in only 48%. In patients pre-diagnosed with arterial hypertension the use of ACE inhibitors is common which therefore most likely affects the test results. Table 1 demonstrates that sIL2-R and neopterin were almost always elevated when tested.

Histological findings

All twenty-seven patients in our study underwent renal biopsy. **Figure 1** elucidates the quantitative distribution of the histological entities found by the pathologist. With 44% the most frequent histological finding in our collective was the non-granulomatous interstitial nephritis (ngIN) followed by granulomatous interstitial nephritis (GIN) in 8 and glomerular disease presenting as IgA glomerulonephritis in 7 cases (30% respectively 26%). In accordance with the small number of six cases of hypercalcemia – as reported above – nephrocalcinosis (NC) was only present in 3 patients (11%). In two cases a combination of GIN and NC and one simultaneous appearance of GIN and IgA-GN were revealed.

Table 2 informs about the three dimensions used to semiquantitatively assess the degree of histological kidney damage. The degree of inflammation is mainly governed by the amount of mononuclear cells infiltrating the interstitial space, as well as the extent of tubulitc lesions. The majority of our pa-

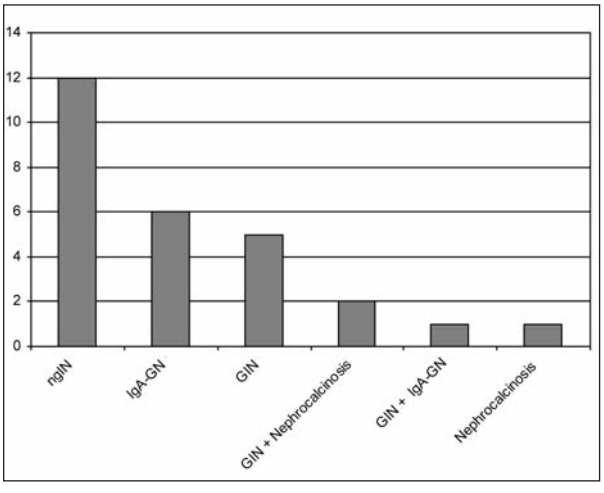

Fig. 1. Quantitative distribution of histological types

Table 2. Histological type and degree of histological kidney damage in comparison with stage of kidney disease

No.	Histological type	Degree of inflammation	Tubular atrophy	Degree of fibrosis	Stage of kidney disease at t0 (CKD)
1	GIN + IgA-GN	1	0	0	1
2	ngIN	1	1	1	1
3	ngIN	1	1	0	4
4	ngIN	1	1	0	3
5	ngIN	1	2	3	3
6	ngIN	1	1	1	3
7	GIN + NC	1	1	1	4
8	ngIN	1	0	0	3
9	GIN	3	0	1	5
10	GIN + NC	1	0	0	5
11	ngIN	3	1	0	3
12	ngIN	1	1	1	1
13	ngIN	1	1	1	4
14	GIN	1	1	0	5
15	GIN	3	1	1	3
16	ngIN	3	0	0	1
17	GIN	2	0	0	3
18	IgA-GN	1	1	2	1
19	IgA-GN	1	1	1	2
20	IgA-GN	1	1	0	1
21	IgA-GN	0	0	0	2
22	IgA-GN	1	0	0	1
23	ngIN	1	1	0	2
24	ngIN	1	1	1	1
25	IgA-GN	1	3	2	2
26	NC	1	1	1	2
27	GIN	1	0	2	5

tients presented with focal inflammation (degree 1, 74%). Extensive tubular atrophy and extensive fibrosis were scarce in our cohort and were only described in one patient each. Most patients presented with less than 33% atrophic tubuli (degree 1, 59%), nine patients had no tubular atrophy at all (33%). In our cohort 85% of patients had no or light fibrosis in renal histology (degrees 0 and 1). Correlation analyses between any of the three histological dimensions to the types of histology remained inconclusive.

As provided by TABLE 2 CKD stage 5 at the patient's initial presentation was solely associated with the histological finding of GIN, and, vice versa, the presence of GIN correlated with higher stages of kidney disease (CKD 3 or higher), i.e. with significantly reduced renal function compared with the other histological entities (p=.017). In contrast, histologically proven IgA-GN went hand in hand with milder stages of kidney function impairment (CKD 1 and 2). Non-granulomatous IN and NC were non-specifically distributed over the 5 stages of kidney disease without showing tendencies to lesser or higher degrees of loss of renal function (FIGURE 2).

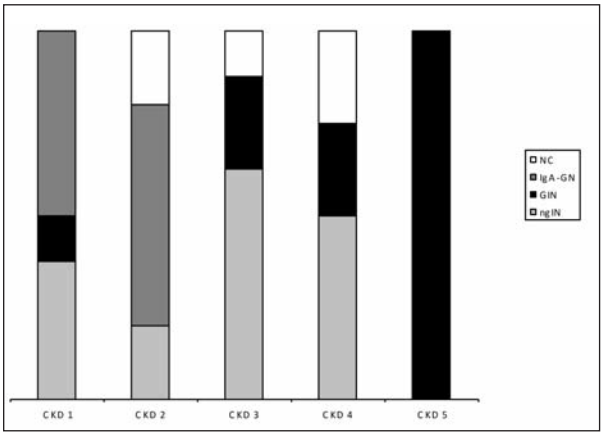

Fig. 2. Distribution of histological entities over different stages of kidney disease

Hypercalcemia favored to appear in cases with either NC or GIN. Accordingly, the one case of a coincidence of NC and GIN also presented with elevated serum calcium levels. Of note, only one patient with ngIN presented with hypercalcemia. However, the small number of hypercalcemic cases does not warrant a powerful statistical statement.

Treatment

All patients were treated with oral prednisone, thirteen (48%) of which with a dose of 1 mg/kg, ten (37%) with 0.5 mg/kg and four patients (15%) with a bodyweight independent fixed dose of 20 mg. The individual dose was at the physician's discretion in charge of the respective patient. In all patients prednisone was applied for 1-2 weeks in the initial dose and was tapered over the upcoming weeks. The mean duration of treatment was 17.4 ± 10.9 weeks after which treatment was either suspended or prednisone doses were reduced to a maintenance dose of 7.5 mg daily or less.

Follow-up period

Of our 27 patients 24 were eligible for follow-up analysis. Kidney function significantly improved at t1 compared to the time when the diagnosis of RS was initially established (i.e. t0) reflecting a significant decrease of creatinine levels from 1.86 ±1.5 to 1.48 ± 1.10 mg/ml (p=.032) and an increase in eGFR from 58 ± 33 to 64 ± 31 ml/min (p=.035). Parallel to this observation proteinuria significantly decreased between t0 and t1 by a mean of 600 mg/24 hrs (p=.011). This decrement in renal protein secretion was still significant when comparing t0 with t3 (p=.023).

As demonstrated in FIGURE 3 kidney function and TPiU did not alter significantly in the further course of the disease for there were no significant changes in neither creatinine levels, GFR nor TPiU between t1 and t2, and t2 and t3 respectively in the overall group.

For a more precise evaluation of kidney function development we separately analyzed patients with CKD stage 1 and those with CKD stages 2 or higher. This seemed imperative since creatinine and GFR are not expected to change in patients that initially present with normal creatinine based kidney function.

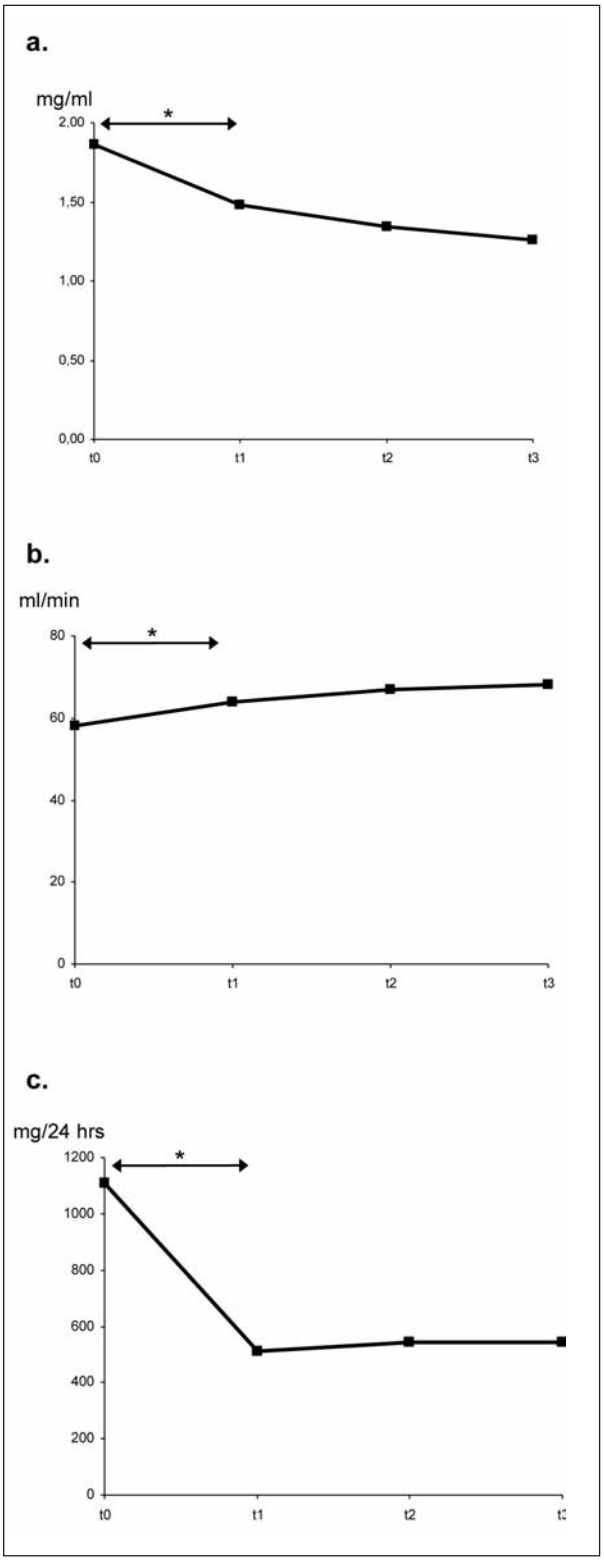

Fig. 3. Course of creatinine (a), GFR (b) and TPiU (c) in all patients

In the subgroup of patients that presented with impaired renal function before commencing therapy mean creatinine levels were 2.4 ± 1.5 mg/dl corresponding with a mean eGFR of 38 ± 21 ml/min at the time of diagnosis. The mean TPiU was 981 ± 304 mg/24 hrs. After commencing therapy the improvement in creatinine levels and GFR again was significant at t1 compared to t0. Creatinine decreased by a mean of 0.6 ± 0.23 mg/ml (p=.024), eGFR improved by a mean of 10 ± 4 ml/min (p=.017) and TPiU declined significantly by a mean of 755 ± 316 mg/24 hrs (p=.036). In the further course of follow up renal function showed further tendencies to improve at t2 and t3. However, as in the overall group, the level of significance was not reached in the comparisons t1/t2 and t2/t3 as shown in FIGURE 4. Mean TPiU levels remained stable in the time between t1 and t3. Nevertheless, at the end of the observation period (i.e. t3) renal function showed a sustained statistically significant amelioration compared to the time of diagnosis. Mean creatinine concentration decreased from 2.4 ± 1.5 to 1.4 ± 0.74 mg/ml (p=.032), mean eGFR increased from 38 ± 21 to 57 ± 21 ml/min (p=.016) and TPiU declined from 981 ± 304 to 176 ± 77 mg/24 hrs (p=.026).

In the smaller subgroup of patients with normal creatinine based renal function at the time of diagnosis (i.e. CKD stage 1) creatinine levels and eGFR were stable over the further course of treatment and follow up. Of note, proteinuria with a mean of 1001 ± 361 mg/24 hrs was similar to that of the group of patients presenting with CKD 2 or greater. In patients with CKD 1 TPiU showed no significant change over time (delta TPiU t0/t3: 343 ± 518 mg/dl, p=.544).

Response to treatment

In the group of patients with impaired renal function at t0 eight out of sixteen patients (50%) responded to prednisone treatment at t1. Five patients (31.3%) fulfilled the criteria of complete response, three patients (18.7%) were partial responders as defined above. In six patients (38%) we noticed an improvement in CKD stage by 1 or more degrees to this time. At the point of the last observation two additional patients improved in CKD stage leading to an overall response rate of 62.5% of patients in

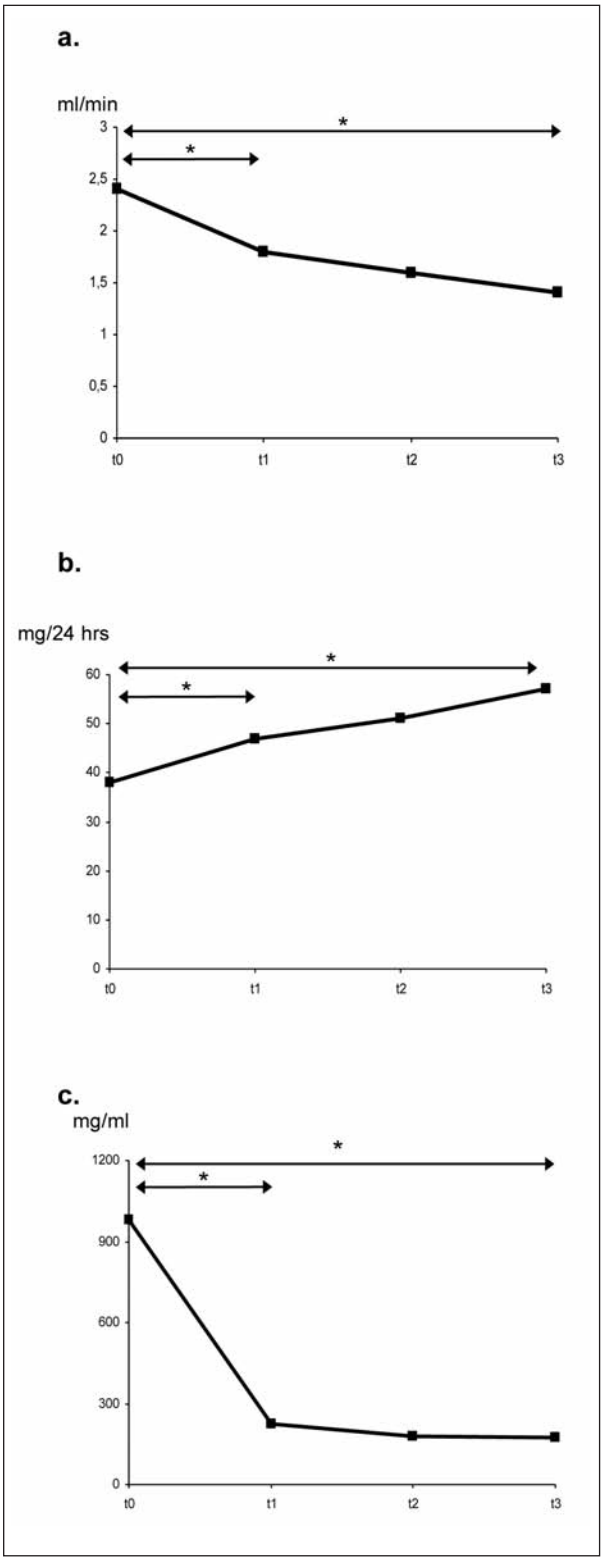

Fig. 4. Course of creatinine (a), GFR (b) and TPiU (c) in patients with CKD stage 2 or higher at initial presentation

this subgroup at the end of follow-up. Accordingly, eight patients (50%) showed either no relevant improvement or deterioration in renal function at t1 (eGFR < 25%). Six of which (38%) remained non-responders at t3.

In the group of patients with an initial CKD stage 1, at t1 four out of five patients (80%) responded to prednisone therapy by showing a reduction of total protein secretion in urine of more than 25% of baseline levels. Three of them were complete responders (TPiU ≥ 50%), one patient was constituted a partial responder (TPiU 25-50%). From the remaining three patients in this subgroup we were unable to obtain data on proteinuria at t1. At the end of follow-up we found an overall response rate of 67% in the CKD 1 subgroup (for 2 patients data on proteinuria was missing at t3).

Correlation analyses between response to treatment and histologic subtypes, degree of fibrosis, inflammatory floridity and tubular atrophy remained inconclusive.

Discussion

In our study we present a cohort of 27 patients with histologically proven RS. It was our goal to present both epidemiological and follow-up data to contribute to the clinical understanding and implications of the disease, as well as to assess the success of therapy.

Despite the fact that sarcoidosis more commonly affects women (14, 22) in case of renal involvement we found in accordance to existing literature a 1.7:1 male predominance while in contrast to other authors the time of disease onset in life was virtually identical between the two genders.

Most of our patients suffered from RS in the context of extra-renal sarcoidosis. We found only 4 cases of isolated RS, which makes isolated RS a rare phenomenon. Still, it has to be considered in interstitial nephritis (IN) if not otherwise explained (5, 7, 25).

One of the main statements of our study is that RS still has to be considered when creatinine based renal function is normal. In these patients special attention has to be paid to proteinuria. According to our data urine sediment is of little help in establishing the diagnosis. Abdominal ultrasound is mostly unremarkable with distinct exceptions like nephrocalcinosis or advanced chronic renal damage.

Renal biopsy is the gold standard in establishing the diagnosis (23). As described by many other authors IN was the predominant histological finding (1, 3, 4, 13, 18, 19, 21). However, in our study most cases were IN without granulomas. For once this might be due to the often debated sampling error (23). On the other hand it can be discussed if the stage of kidney disease the patient presents with might be relevant. In this study, many patients with ngIN presented with normal or only moderately decreased kidney function whereas patients with GIN significantly tended to be those with CKD stages 3 and above. Furthermore, all our patients staged CKD 5 at the time of diagnosis had histological evidence of GIN. It could be argued that in advanced renal insufficiency the renal load of granulomas is that high it makes them more likely to be detected by biopsy, while in earlier stages of kidney damage with a lesser load of granulomas and due to the focal nature of the inflammation these are more often missed by biopsy. Vice versa, in cases of IgA-nephritis kidney function was never worse than CKD stage 2 in our study.

In our opinion the diagnosis of RS must not be discarded in absence of granulomas, especially in patients with normal or moderately impaired renal function.

Laboratory tests like ACE, sIL2-R and neopterin can help in establishing the diagnosis but they are more suited to be parameters of disease activity. Normal ACE levels do not exclude the presence of sarcoidosis, whereas according to our findings sIL2-R and neopterin might be more reliable. Nearly all patients had elevated levels of sIL2-R and/or neopterin if yet they were only tested in a small portion of patients, which does not warrant a sound statistical statement.

Prednisone is the cornerstone of treatment in all forms of sarcoidosis. Mahévas and Rajakariar with their respective co-workers have demonstrated the efficacy of prednisone in RS in larger cohorts (18, 21). Apart from these two studies literature mostly offers single case reports and small case series. To our knowledge there is no controlled randomized study regarding RS treatment so far. In our retrospective analysis we followed up 24 patients over at least 2 years. We confirm previous findings that prednisone therapy significantly improves renal function and re-

duces proteinuria after 6-12 weeks. Beyond that point eGFR can still further improve, however levels of significance were no longer achieved. This leads to the conclusion that early response to therapy is a prognostic factor for renal recovery in RS as others have proposed (18, 21). Nevertheless, complete response as defined above (in accordance with Mahévas) was observed only in about 31% of our cases. At the end of the observation period roughly 63% of patients showed an increase in kidney function of at least 25% to baseline levels, all but two of which achieved their improvement within the first 6-12 weeks. According to our data we argue that an early response to treatment is crucial in terms of long-term outcome. Mahévas and Rajakariar further established the degree of fibrosis as a prognostic factor (18, 21). Our data does not echo this proposal since we found no significant correlation between the histological extent of renal damage and the degree of renal function impairment. Firstly, it could be argued that immune cell infiltration of the kidney is not homogenous but shows focal variance in that we are again looking at a sampling problem. Secondly, one might speculate that not only the amount of infiltrating lymphocytes but also the time between disease onset and diagnosis, reflecting the lapse of time the disease is untreated, is of relevance. Yet, our study was not designed to answer that question.

In patients with CKD stage 1 at the time of diagnosis prednisone treatment was able to preserve renal function and to reduce proteinuria although TPiU was not significant due to a lack of power in this subgroup.

Albeit most patients with initially impaired creatinine based renal function showed improvement under therapy only two patients (12.5%) achieved a complete recovery of renal function to an eGFR ≥ 90 ml/min. This underlines the importance of a consequent steroid treatment of RS. It also ignites the discussion whether an additional steroid sparing immunosuppression is necessary in primary therapy to facilitate a long standing, non-steroid based therapy. In most centers immunosuppressants other than steroids are enrolled in the event of relapse. MTX has been successfully tested in a double-blinded randomized trial in acute sarcoidosis (2), however, since MTX is contraindicated in impaired renal function it does not seem to be suitable for RS. There are single case reports of the successful use of azathioprine, mycofenolate mofetil and infliximab (10, 27). Our patients in total were on 0.5 - 1 mg/kg prednisone only. We did not observe any RS related relapses in our cohort.

In summary we strongly recommend considering RS in all patients with extra-renal manifestations of sarcoidosis, even in cases where creatinine based kidney function is normal. The diagnosis is to be established by renal biopsy. Isolated RS is rare but must be kept in mind if the histological pattern cannot be otherwise interpreted. GIN in direct contrast to IgA-GN is associated with more severe renal function impairment at baseline. Prednisone treatment seems to be effective in preserving respectively improving renal function and in reducing proteinuria. According to our data the key prognostic factor for renal recovery seems to be an early response to therapy.

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