

IgA nephropathy in patients with spondyloarthritis followed-up at the Rheumatology Service of Hospital das Clínicas/UFMG

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ABSTRACT

Objective: To determine the frequency of glomerulonephritis in patients with spondyloarthritis followed-up at a Brazilian Rheumatology Service, and to evaluate the clinical variables associated. **Patients and methods:** Patients were assessed for sociodemographic characteristics, type of spondyloarthritis, time since diagnosis and disease activity, non-steroidal anti-inflammatory drug use, HLA-B27 positivity, creatinine and urea serum levels, major comorbidities, hematuria and proteinuria. Patients with hematuria were subsequently assessed for the presence of dysmorphic red blood cells in urine, and those with proteinuria underwent 24-hour urine protein measurement. Renal biopsy was performed in patients with glomerular hematuria and/or proteinuria over 3.5 g/24-hour. **Results:** Seventy-six patients were assessed. Microscopic hematuria was the most frequently found abnormality in urinalysis (44.7%), usually intermittent and in spot urine samples during patients' follow-up. In eight patients (10.5%), glomerular hematuria was suspected. Renal biopsy was performed in five of them, showing IgA nephropathy in four (5.3%) and thin membrane disease in one patient. **Conclusions:** A high frequency of urinalysis alterations was observed in that subgroup of patients, as well as a high prevalence of IgA nephropathy. Although further studies on this subject are needed to better clarify these results, periodic urinalysis of patients with spondyloarthritis should be recommended.

Keywords: glomerulonephritis, spondyloarthropathies, IgA glomerulonephritis, hematuria.

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INTRODUCTION

Screening for glomerulonephritis (GN) in patients with spondyloarthritis (SPA) is not routinely recommended.^{1,2} However, a higher frequency of renal impairment in SPA has been reported.^{3,4} The types of renal impairment reported are as follows: renal amyloidosis, nephropathy related to non-steroidal anti-inflammatory drugs (NSAIDs), extracapillary GN due to treatment with anti-tumor necrosis factor

(anti-TNF), membranous GN, and mesangial IgA GN.³⁻¹⁵ There is a hypothesis that IgA nephropathy and ankylosing spondylitis might share etiopathogenic mechanisms.¹⁶

GN comprise a large variety of immune mediated changes that cause inflammation mainly in the renal glomerulus. They are the second cause of end-stage renal disease worldwide.¹⁷ The clinical presentation of GN comprises the constant presence of proteinuria and/or hematuria, which may or may not be accompanied by other symptoms or clinical signs.¹⁸

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This study aimed at studying the prevalence of GN in patients with SPA followed-up at the Rheumatology Service of Hospital das Clínicas/Universidade Federal de Minas Gerais (HC/UFMG), in addition to trying to correlate the presence of GN with SPA duration, characteristics, and activity.

PATIENTS AND METHODS

Patients with SPA over the age of 18 years were assessed according to the European Spondyloarthropathy Study Group criteria¹ and followed-up at the Spondyloarthritis Outpatient Clinic of the Rheumatology Service of HC/UFMG for at least one year, from September 2007 to February 2009. In that outpatient clinic, routine urinalysis is requested at every medical visit. In addition, the presence of hematuria and/or proteinuria was assessed in previous routine urinalysis. Hematuria was considered as the presence, under optical microscopy, of more than two red blood cells at higher magnification of the urinary sediment, or a positive urinalysis reagent strip.¹⁹⁻²¹ In routine urinalysis, proteinuria was considered as either positive semiquantitative tests for protein or proteinuria greater than 150 mg/dL in 24-hour urine.²²

Patients with hematuria underwent urinary sediment analysis and screening for dysmorphic erythrocytes at a reference laboratory (technically possible in patients with at least nine red blood cells per higher magnification field under optical microscopy). Patients with proteinuria underwent proteinuria quantification in 24-hour urine.

In addition to the assessment for changes in urine test, patients were also assessed for their social, demographic and economic characteristics; SPA characteristics [duration of disease from diagnosis, disease activity in patients with a predominance of axial impairment according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)];²³ medications used for treatment, and, in the case of NSAIDs, the duration of their use; HLA-B27 positivity (by use of any laboratory investigation method); renal function assessment (serum creatinine and urea); inflammatory activity (C-reactive protein measurement); and diagnosis of clinical comorbidities, especially systemic arterial hypertension (SAH), defined according to the criteria of the Joint Committee on Detection, Evaluation and Treatment of High Blood Pressure – JNC VII,²⁴ and chronic renal failure (CRF), defined as glomerular filtration fraction lower than 60 mL/min/1.73 m² for three months or more. Other relevant comorbidities reported in the medical records were also considered.

Ultrasound-guided renal biopsy was indicated in patients with the following findings: hematuria confirmed

on the urinary sediment exam, with a glomerular origin suggested (presence of red blood cell casts and/or 80% or more of dysmorphic erythrocytes), and/or isolated proteinuria greater than 3.5 g in 24-hour urine, which is defined as nephrotic proteinuria and strongly indicates the presence of glomerulopathy.¹⁸

Renal biopsy was contraindicated in patients with untreatable hemorrhagic diathesis, kidneys smaller than 9 cm on urinary tract ultrasound, severe SAH despite the use of anti-hypertensive drugs, bilateral and multiple renal cysts, renal neoplasia, hydronephrosis, non-treated renal or perirenal infection, non-cooperative patients, and patients refusing to undergo the procedure.

The exclusion criteria were patients under the age of 18 years and those refusing to participate in the study.

The chi-square test or Fisher's exact test were used to assess categorical variables. For continuous variables, Student's *t* test was used for those with characteristics of normality, and the non-parametric Mann-Whitney test was used for those without such characteristics. The significance level adopted in all analyses was 5% ($P < 0.05$). Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS®) software, version 16.0 (SPSS Inc., Chicago, IL, USA).

The project was approved by the Research Ethics Committee of UFMG (ETIC No. 086/07) and by the Board of Education, Research and Extension of HC/UFMG (Case No. 142/2006).

RESULTS

This study assessed 76 patients with SPA, whose major characteristics are listed in Table 1. Of the patients studied, HLA-B27 could be assessed in 51, being positive in 33 (43.4%).

The mean BASDAI (ranging from zero to ten) found was 3.86 ± 2.06 (minimum of zero and maximum of 7.64). C-reactive protein was also measured, aiming at assessing disease activity, with a median of 6, and 25 and 75 percentiles of 3 and 19.6, respectively.

Regarding the medicamentous treatment, most patients studied (82.9%) were on NSAIDs for a mean period of 6.5 ± 6.2 years (range: from zero to 29 years).

Microscopic hematuria was detected in at least one routine urine test of 34 individuals (44.7%), and on more than one occasion in 22 individuals (28.9%). Most patients (22.4%) with hematuria on more than one occasion had intermittent hematuria. Continuous hematuria occurred in only five patients (6.5%). Gross hematuria was less frequent than the microscopic one, occurring in 13 patients (17.1%).

Table 1
Characteristics of the population studied

	N (%)
Gender	
Male	49 (64.5)
Age	
Mean = 42.7 years; minimum, 22; maximum, 75	
White	53 (69.7)
Monthly income < 3 minimum wages	68 (89.5)
Years of study	
Median = 8	
Comorbidities	
SAH	29 (38.2)
CRF	2 (2.6)
Diabetes mellitus	2 (2.6)
Positive serology for HIV	Zero
Liver disease	1 (1.3)
Drugs used to treat SPA	
NSAIDs	63 (82.9)
Oral corticoid	34 (44.7)
Methotrexate	26 (34.2)
Sulfasalazine	1 (1.3)
Anti-TNF α inhibitor	1 (1.3)
Prevalence of SPA types	
Ankylosing spondylitis	47 (61.8)
Undifferentiated spondyloarthritis	11 (14.5)
Psoriatic arthritis	11 (14.5)
Reactive arthritis	4 (5.3)
Arthritis of inflammatory bowel diseases	3 (3.9)
Associated articular and extra-articular clinical manifestations	
Calcaneal enthesitis	38 (50)
Anterior uveitis	29 (38.2)
Coxarthrosis	21 (27.6)
Dactylitis	9 (11.8)
Pulmonary fibrosis	1 (1.3)
Sterile pyuria	1 (1.3)

SPA: spondyloarthritis; SAH: systemic arterial hypertension; CRF: chronic renal failure; NSAIDs: non-steroid anti-inflammatory drugs.

Of the 24 patients assessed for presence of dysmorphic erythrocytes, eight (10.5%) had dysmorphic changes in more than 80% of their red blood cells. Of these eight patients, five underwent renal biopsy, while three refused to undergo the procedure. The histopathological results were as follows: IgA nephropathy in four patients (5.2%) and thin membrane disease (benign familial hematuria) in one patient. The characteristics of patients with IgA nephropathy are shown in Table 2.

Other causes of hematuria, except for GN, were as follows: nephrolithiasis, five patients (6.5%), one of whom also had IgA nephropathy; polycystic kidney, one patient (1.3%); and hematuria of gynecological origin, one patient (1.3%). In 20 patients (26%), the etiology of hematuria remained undetermined.

Proteinuria was not common in the sample studied, being detected in only three patients (3.9%), two of whom had proteinuria greater than 3.5 g in 24 hours. These three patients also had hematuria. No patient had isolated proteinuria.

The presence of hematuria was neither associated with the type of SPA ($P > 0.20$) nor disease activity, measured by either CRP ($P = 0.954$) or BASDAI ($P = 0.251$). HLA-B27 antigen positivity did not associate with the presence of hematuria ($P = 0.251$). No statistically significant association was found between microscopic hematuria and CRF ($P = 1$), SAH ($P = 0.81$), proteinuria ($P = 0.85$) and increased creatinine serum levels ($P = 0.40$).

The use of NSAIDs in this sample showed no positive association with the increase in creatinine serum levels ($P = 0.318$), even when taking into account their time of use ($P = 0.582$). In addition, no statistically significant association was found between the use of NSAIDs and the presence of CRF ($P = 0.31$), hematuria ($P = 1$), proteinuria ($P = 0.74$) and SAH ($P = 1$).

Table 2
Characteristics of the patients undergoing renal biopsy diagnosed with IgA nephropathy

Patients	1	2	3	4
Gender	Male	Male	Male	Male
Age	36	43	33	44
SPA type	Reactive arthritis	Ankylosing spondylitis	Ankylosing spondylitis	Ankylosing spondylitis
SPA duration (years)	16	27	9	19
HLA-B27	Positive	Positive	Positive	Positive
Creatinine (mg/dL)	1.01	2.85	0.6	0.8
24-hour proteinuria (mg/dL)	300	2,350	173	1,900
SAH	No	No	No	Yes

SPA: spondyloarthritis; SAH: systemic arterial hypertension.

DISCUSSION

The present study assessed the frequency of GN in patients with SPA followed-up at the Rheumatology Service of HC/UFMG, in the city of Belo Horizonte, state of Minas Gerais.

The clinical characteristics of the patients assessed in this study did not differ from those reported in the literature.^{1,25-33} Most patients were male, and ankylosing spondylitis was the most frequently found form of SPA, followed by undifferentiated SPA and psoriatic arthritis. Recent studies show a reversal of this relationship, with a higher prevalence of undifferentiated SPA than ankylosing spondylitis.²⁸ There was a higher frequency of calcaneal enthesitis among the associated manifestations and of anterior uveitis among the extra-articular manifestations. Positivity for HLA-B27 was observed in 43.4% of the population studied. Unfortunately, comparing such data with those of other populations is difficult because most studies assess the frequency of this antigen in patients with ankylosing spondylitis and not in those with SPA.^{34,35}

This study showed a high frequency of changes on the urinalysis of patients with SPA. The most commonly found was microscopic hematuria on a single occasion, which occurred in 34 patients (44.7%). In 22 of these patients (28.9%), hematuria was evidenced in two or more urine samples, 17 (22.4%) of whom had intermittent hematuria, not occurring in all urinalyses. Continuous hematuria was found in only five patients (6.5%). The high prevalence of hematuria in this population may have resulted from the definition of hematuria adopted in the methodology (two or more red blood cells per field), which favored the sensitivity of the test, because the initial objective was to screen patients for urinary sediment analysis and dysmorphic erythrocyte identification at a reference laboratory. In the general population, the prevalence of any type of hematuria (single occasion, intermittent, or continuous) ranges from 0.18% to 16.1%, being relatively common in adults and not usually indicating the presence of a disease, often being an incidental finding.^{19,36-39} Hematuria can result from physical exercise, sexual intercourse in the two days preceding sample collection, and use of anticoagulant agents. The most common pathological causes are abnormalities of the low urinary tract (especially those affecting the urethra, prostate, and urinary bladder). In less than 10% of the cases, hematuria is of glomerular origin,¹⁹ its major etiologies being IgA nephropathy and thin membrane disease (benign familial hematuria).⁴⁰

The origin of hematuria, whether glomerular or not, should be identified. In the population studied, eight (10.5%) patients had glomerular hematuria. Proteinuria, however, was

not frequent (3.9%), and always occurred in association with hematuria, emphasizing its probable glomerular origin.

In this study, the presence of hematuria did not correlate with the type of SPA; HLA-B27 antigen presence; and disease activity. In addition, no association was observed between hematuria and SAH, proteinuria, and increased creatinine serum levels.

The indication of renal biopsy in patients with isolated microscopic hematuria is controversial. In the presence of hematuria with a strongly suggestive glomerular origin, and considering the individual risks and benefits, only renal biopsy can lead to the definitive diagnosis of GN.^{41,42} Thus, in patients with SPA, usually using NSAIDs and with hematuria of glomerular origin, renal biopsy was considered justifiable.

Of the 76 patients assessed, four (5.2%) had GN with characteristics of mesangial proliferative glomerulopathy with IgA immune deposits, characterizing IgA GN or Berger's disease. However, the prevalence of IgA GN in the patients studied may have been underestimated, because intermittent microscopic hematuria hinders the search for dysmorphic erythrocytes and the confirmation of the glomerular origin of hematuria. In addition, three patients suspected of having GN refused to undergo renal biopsy. This finding is not in accordance with the prevalence of IgA nephropathy in the general population, estimated at 25 to 50 cases per 100,000 individuals.^{43,44}

The literature about renal changes in patients with SPA is scarce and mostly based on case series. Although controversial, the greatest occurrence of IgA GN in patients with SPA has been often considered.⁵⁻⁷ In 1987, Jones et al.⁷ assessed the renal function of 51 patients with ankylosing spondylitis randomly selected in rheumatology clinics. Of these 51 patients, five (10%) had persistent abnormalities (on more than one occasion) in testes performed to assess renal function (microscopic hematuria in all five patients, decreased renal function and increased 24-hour proteinuria in four of them). In the three patients undergoing renal biopsy, the results were as follows: focal segmental glomerulosclerosis with negative immunofluorescence, one patient; IgA nephropathy, one patient; and interstitial cellular infiltrate with both tubular fibrosis and atrophy, and negative immunofluorescence and electron microscopy, one patient.

In Brazil, there was an attempt to assess the frequency and severity of renal impairment in 40 patients with ankylosing spondylitis followed-up at a clinic specialized in rheumatology. In that sample, 14 (35%) patients had one or more signs of renal involvement; nine patients had hematuria, six of whom with dysmorphic erythrocytes; four patients had microalbuminuria;

two had an increase in creatinine serum levels; and four had a reduction in creatinine clearance. Statistically significant association was neither observed between microscopic hematuria and disease activity or duration nor between microscopic hematuria and serum IgA levels. However, significant association was observed between microscopic hematuria and the reduction in creatinine clearance.⁴ These patients have not undergone renal biopsy.

Another type of renal impairment in patients with SPA is the one resulting from the regular use of NSAIDs.³⁻⁷ In the general population, 1% to 5% of the patients developed renal adverse effects related to medical intervention involving NSAIDs. The renal problems attributed to the use of these medications are acute renal failure, nephrotic syndrome with interstitial nephritis, and acute and chronic papillary necrosis.⁴⁵ In the present study, almost all patients (82.9%) regularly used these medications and for a prolonged time (mean of 6.5 years). However, no renal adverse effect from the use of NSAIDs

was detected in our patients. In addition, the use of NSAIDs was not positively associated with the increase in creatinine serum levels or the presence of hematuria, proteinuria, CRF, and SAH. This might have resulted from the low frequency of comorbidities that predispose to the adverse effects of NSAIDs in our study population, such as advanced age, liver disease, heart failure, and renal failure.⁴⁵ Another explanation for this finding would be the standard practice at the Rheumatology Outpatient Clinic to avoid the use of NSAIDs in patients with any of these comorbidities.

This study shows the high frequency of changes found in the urinalysis of a subgroup of patients with SPA, as well as the high prevalence of IgA nephropathy. Thus, although further studies on this subject are required to better clarify the renal changes in patients with SPA, periodical urinalysis should be recommended. The definitive diagnosis of GN in this group is extremely relevant, considering the implications in the treatment of SPA and the prognosis of these patients.

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