Rheumatol Int (2013) 33:1689–1692
DOI 10.1007/s00296-012-2624-9

ORIGINAL ARTICLE

Renal involvement in ankylosing spondylitis: prevalence, pathology, response to TNF-a blocker

Sang-Hoon Lee · Eun Jung Lee · Sang Wan Chung · Ran Song · Joo-Young Moon · Sang-Ho Lee · Sung-Jig Lim · Yeon-Ah Lee · Seung-Jae Hong · Hyung-In Yang

Received: 8 June 2012 / Accepted: 9 December 2012 / Published online: 27 December 2012

Abstract Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily involving the spine and sacroiliac joint and rarely the kidneys. This study aimed to define the clinical and histological features and biology of renal disease in AS. We reviewed the medical records of 681 patients diagnosed with AS from November 2008 to November 2009. Baseline characteristics and laboratory and urinalysis results were reviewed. We identified patients with proteinuria or hematuria and analyzed their risk factors. After providing informed consent, 6 patients underwent a renal biopsy to determine the cause of proteinuria or hematuria. Of the 681 enrolled patients, 547 were men and 134 were women; 81 % were HLA B27 positive, and 8 % had abnormal urinalysis findings (proteinuria, 5.9 %; hematuria, 2.8 %; both, 0.7 %). Incidences of peripheral arthritis and uveitis were 29 % and 18.6 %, respectively. Immunoglobulin (Ig)A and uric acid levels were significantly different between patients with and without proteinuria. Erythrocyte sedimentation rate (ESR), total cholesterol, creatinine, and C-reactive protein (CRP) levels were not statistically significantly different between the 2 groups nor were there any significant differences in IgA, uric acid, ESR, total cholesterol, creatinine, and CRP levels between patients with and without hematuria. Six patients who had >1 g/day proteinuria underwent a renal biopsy; 2 were diagnosed with IgA nephropathy, 1 with amyloidosis, and 3 with non-specific glomerulonephropathy. In the amyloidosis patient, severe proteinuria was the dominant feature. For patients with renal amyloidosis and other forms of glomerulonephritis who initially had normal creatinine levels, tumor necrosis factor (TNF)-alpha blocker therapy resolved proteinuria, but this was not the case for patients with initial renal insufficiency. Renal involvement is not a rare complication of AS, and prognoses differ depending on kidney pathology. Serum levels of uric acid and IgA may predict renal involvement in AS. In cases where abnormal urine sediment is identified, renal biopsy is required to determine prognosis and decide the treatment protocol. Baseline serum creatinine level is important for predicting treatment response.

Keywords Ankylosing spondylitis · Kidney · Tumor necrosis factor inhibitor

S.-H. Lee (✉)
Department of Rheumatology, Hospital at Gang Dong, Kyung Hee University, 149 Sangil-dong, Gangdong-gu, Seoul 134-727, South Korea
e-mail: boltaguni@yahoo.co.kr

S.-H. Lee · E. J. Lee · S. W. Chung · R. Song · H.-I. Yang
Department of Rheumatology, Hospital at Gang dong, School of Medicine, Kyung Hee University, Seoul, South Korea

J.-Y. Moon · S.-H. Lee
Department of Nephrology, Hospital at Gang dong, School of Medicine, Kyung Hee University, Seoul, South Korea

S.-J. Lim
Department of Pathology, Hospital at Gang dong, School of Medicine, Kyung Hee University, Seoul, South Korea

Y.-A. Lee · S.-J. Hong
Department of Rheumatology, Medical Center, School of Medicine, Kyung Hee University, Seoul, South Korea

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton and is manifested by back pain and progressive stiffness of the spine. AS is the most frequent and most severe subtype of spondyloarthropathies,

and it can be an outcome of any of the other spondyloarthropathy subtypes [1]. The prevalence of AS varies from 0 to 1.4 %, depending upon ethnic group, prevalence of HLA B27, selection of subjects for evaluation, and criteria for diagnosis [2–6]. AS primarily affects the axial joints, most notably the sacroiliac joints (this pain is regarded as the hallmark of AS). Other sites of involvement include the spine, peripheral joints, and entheses (capsules, ligaments, and tendons) [1, 7]. In addition, the involvement of several other organ systems may occur, and many epidemiological studies have found higher incidences of extraarticular manifestations to be a consequence of uncontrolled systemic inflammation [8]. Screening for extraarticular manifestations in patients diagnosed with AS is important to ensure appropriate management because the presence of extraarticular manifestations may influence treatment decisions [9]. The most common extraarticular manifestations are uveitis, bowel disease, and involvement of the heart, lung, skin, bone, and kidney. However, the mechanism underlying such involvement is unknown. Renal involvement in AS, although uncommon, may include secondary renal amyloidosis (AA type), non-steroidal anti-inflammatory drug (NSAID) nephropathy, and glomerulonephritis [10–12]. However, the true prevalence of renal involvement in AS patients is unknown, and no study has examined a large group of AS patients. Our center treats a relatively large number of patients with AS, and we designed this study to evaluate and define the clinical and histological features of renal disease in AS and its response to treatment.

Materials and methods

This study was performed at a single center.

We reviewed the medical records of 681 patients diagnosed with AS according to the modified New York criteria from November 2008 to November 2009 at Kyung Hee Hospital in Gandong, Seoul, South Korea. We reviewed sex, age, disease duration, presence of HLA B27, extraarticular manifestations, and results of laboratory examination and urinalysis. We defined abnormal renal involvement as proteinuria or hematuria of at least grade 1+ detected on at least 2 consecutive examinations. Once patients with proteinuria or hematuria were identified, and their risk factors were evaluated relative to the abnormal urinalysis results. Patients with proteinuria of >grade 1+ were selected for further study. If proteinuria was >1 g/day after 24-h urine collection, a renal biopsy was performed once the patients had provided informed consent. Six patients underwent a renal biopsy to determine the cause of proteinuria or hematuria.

Statistical analysis

SPSS (version 11.5) was used for statistical analysis. The data are expressed as mean ± SD. The baseline differences between the groups were tested using Student's t test and a χ^2 test; $P < 0.05$ was considered significant.

Results

Baseline characteristics

A total of 681 patients were enrolled in the study, including 547 men and 134 women; 81 % of the patients were HLA B27 positive, and abnormal urinalysis findings were detected in 8 % (proteinuria, 5.9 %; hematuria, 2.8 %; both, 0.7 %). Peripheral arthritis was identified in 29 % of patients and uveitis in 18.6 % (Table 1).

IgA and uric acid levels were significantly different between patients with and without proteinuria. The erythrocyte sedimentation rate (ESR), total cholesterol, creatinine, and C-reactive protein (CRP) levels were not statistically significantly different between the groups (Table 2). In addition, there was no significant difference in levels of IgA, uric acid, ESR, total cholesterol, creatinine, and CRP between patients with and without hematuria (Table 3). Six patients who had >1 g/day of proteinuria underwent a renal biopsy; 2 were diagnosed with IgA nephropathy, 1 with amyloidosis, and 3 with nonspecific glomerulonephropathy (Table 4). In the amyloidosis patient, severe proteinuria was the dominant feature. In the patient with renal amyloidosis, tumor necrosis factor (TNF)-alpha blocker therapy resolved proteinuria, but this was not the case among those with IgA nephropathy.

Table 1 Baseline characteristics and clinical features of patients with AS

Characteristics	Patients ($n = 681$)
Age (mean ± SD)	34.33 ± 10.96
Disease duration (year)	8.53 ± 7.71
Male (n)	547
Positive HLA B27 (%)	550 (80.8)
Uveitis (%)	127 (18.6)
Peripheral joint involvement (%)	198 (29.1)
Urinalysis abnormality (%)	55 (8.1)
Proteinuria (%)	41 (6)
Hematuria (%)	19 (2.8)
Proteinuria and hematuria (%)	5 (0.7)

Table 2 Clinical features based on the presence of proteinuria

	Proteinuria (+) ($N = 41$)	Proteinuria (−) ($N = 640$)	p value
Age (mean ± SD)	31.44 ± 8.42	34.51 ± 11.08	0.08
Disease duration (year)	8.71 ± 6.69	8.52 ± 7.78	0.88
Male (*n*)	37	510	0.09
Positive HLA B27 (*n*)	34	516	0.48
Uveitis (*n*)	12	115	0.07
Peripheral joint involvement (*n*)	17	181	0.07
ESR (mm/h)	12.32 ± 11.95	10.30 ± 11.42	0.27
IgA (mg/dL)	289.37 ± 98.96	246.99 ± 95.71	0.006
Total cholesterol (mg/dL)	173.24 ± 35.93	181.45 ± 35.56	0.15
Uric acid (mg/dL)	5.95 ± 1.59	5.42 ± 1.51	0.03
Creatinine (mg/dL)	0.93 ± 0.21	0.92 ± 0.16	0.77
C-reactive protein (mg/dL)	0.59 ± 0.71	0.54 ± 1.11	0.76

Table 3 Clinical features based on the presence of hematuria

	Hematuria (+) ($N = 19$)	Hematuria (−) ($N = 662$)	p value
Age (mean ± SD)	31.37 ± 8.13	34.41 ± 11.02	0.23
Disease duration (year)	9.68 ± 6.01	8.50 ± 7.76	0.50
Male (*n*)	13	534	0.18
Positive HLA B27 (*n*)	16	534	0.2
Uveitis (*n*)	4	123	0.78
Peripheral joint involvement (*n*)	9	189	0.07
ESR (mm/h)	9.74 ± 8.58	10.44 ± 11.53	0.79
IgA (mg/dL)	246.74 ± 89.28	249.63 ± 96.63	0.89
Total cholesterol (mg/dL)	174.32 ± 30.91	181.15 ± 35.74	0.41
Uric acid (mg/dL)	5.34 ± 1.22	5.46 ± 1.53	0.73
Creatinine (mg/dL)	0.92 ± 0.21	0.92 ± 0.16	0.98
C-reactive protein (mg/dL)	0.61 ± 0.86	0.54 ± 1.09	0.77

Table 4 Characteristics of patients who underwent a renal biopsy

		Dur (year)	Onset age	HLA B27	Uveitis	Peripheral joint	IgA	Proteinuria (initial, f/u)	Hematuria (initial, f/u)	Cr	Biologics	Pathology
Pt 1	M/29	12	17	B2705	−	−	625	3+, 3+	3+, 3+	1.6	Infliximab	IgAN
Pt 2	F/25	8	17	B2705	−	+	237	2+, +−	1+, 1+	0.8	Infliximab	Chronic GN
Pt 3	F/31	3	28	B2705	−	+	189	3+, −	−, −	0.6	Etanercept	Amyloidosis
Pt 4	M/37	19	18	B27	−	−	468	2+/+−	3+/1+	1.6	Adalimumab	Thin GBM
Pt 5	M/31	24	7	B2705	−	+	186	2+/+−	3+/3+	1	Etanercept	Chronic GN
Pt 6	M/30	7	23	B2705	−	−	425	3+, −	2+, +−	1	Adalimumab	IgAN

Discussion

To the best of our knowledge, the current review of renal involvement involves the largest number of patients with AS to date. Our data revealed that renal abnormality among AS patients is not rare (8 %). The incidence of renal abnormalities (including glomerulonephritis and particularly disorders associated with the deposition of IgA-containing immune complexes, renal amyloid deposition, microscopic hematuria, microalbuminuria, and decreased renal function and creatinine clearance) has been shown to range from 10 to 30 % in patients with AS [9]. Among our patients, proteinuria was found in 5.9 % of patients, hematuria in 2.8 %, and both in 0.7 %. Only serum IgA and uric acid levels were significantly higher in the proteinuria group than in the non-proteinuria group. It was unclear whether proteinuria was the cause of the high levels of IgA and uric acid or whether high IgA and uric

acid levels caused proteinuria. Amyloidosis is more prevalent in aggressive and active AS and among older patients with long-standing disease [13]. However, our patient had a relatively short disease duration of 3 years. A Finnish hospital-based study of patients with AS with a mean follow-up time of 25 years demonstrated an overall mortality rate 1.5 times higher than expected, which was explained by a high incidence of deaths from AS, mainly due to AA amyloidosis [14]. Our patient with renal amyloidosis was also of the AA type. Some case reports have suggested that TNF-inhibitors play a role in alleviation of AA amyloidosis [15]. Our patient improved, and after being treated with etanercept for 12 months, proteinuria decreased from 3,702 to 200 mg/day. In the 2 patients with IgA glomerulonephritis, proteinuria and hematuria were present. One patient was treated with infliximab, but proteinuria was not alleviated although his BASDAI score and CRP level were normalized. His initial serum creatinine level was 1.6 mg/dL. The other patient was treated with adalimumab, and his proteinuria was alleviated; this patient's initial serum creatinine level was 1.0 mg/dL. Patients 2 and 5 may have had IgA nephropathy, but biopsy may have shown presence of chronic glomerulonephritis because they had proteinuria with hematuria. Proteinuria was alleviated in the patient with an initially normal serum creatinine level, but this was not the case for the proteinuria of the patient with thin glomerular basement membrane disease. His initial serum creatinine level was 1.6 mg/dL. These results suggest that initial creatinine level is important for predicting the response to a TNF-alpha blocker. One limitation of this study was that our data were not prospective. However, patients were followed up for at least 1 year after biopsy.

Our findings suggest that renal involvement is not a rare complication of AS and that prognoses differ depending on kidney pathology. We suggest that serum levels of uric acid and IgA predict renal involvement in AS. For patients in whom abnormal urine sediment is identified, a renal biopsy should be performed to evaluate the prognosis and to determine the treatment protocol. In addition, baseline serum creatinine level is important for predicting treatment response.

Acknowledgments This study was funded by the program of the Kyung Hee University for the young professor in 20071400.

References

1. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A (2002) Ankylosing spondylitis: an overview. Ann Rheum Dis 61(suppl 3):iii8–iii18
2. Lawrence RC, Helmick CG, Arnett FC et al (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthr Rheum 41:778–799
3. Khan MA (1995) HLA-B27 and its subtypes in world populations. Curr Opin Rheumatol 7:263–269
4. Braun J, Bollow M, Remlinger G et al (1998) Prevalence of spondyloarthropathies in HLA-B27 positive and negative blood donors. Arthr Rheum 41:58–67
5. Ng SC, Liao Z, Yu DT et al (2007) Epidemiology of spondyloarthritis in the People's Republic of China: review of the literature and commentary. Semin Arthr Rheum 37:39–47
6. Helmick CG, Felson DT, Lawrence RC et al (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthr Rheum 58:15–25
7. El Maghraoui A (2004) Ankylosing spondylitis. Press Med 33:1459–1464
8. Elewaut D, Matucci-Cerini M (2009) Treatment of ankylosing spondylitis and extra-articular manifestations in everyday rheumatology practice. Rheumatology(Oxford) 48:1029–1035
9. El Maghraoui A (2011) Extra-articular manifestations of ankylosing spondylitis: prevalence, characteristics and therapeutic implications. Eur J Intern Med 22:554–560 (Review)
10. Vilar MJP, Cury SE, Ferraz MB, Sesso R, Atra E (1997) Renal abnormalities in ankylosing spondylitis. Scand J Rheumatol 26:19–23
11. Nabokov AV, Shabunin MA, Smirnov AV (1996) Renal involvement in ankylosing spondylitis (Bechterew's disease). Nephrol Dial Transpl 11:1172–1175
12. Strobel ES, Fritschka E (1998) Reanl diseases in ankylosing spondylitis: review of the literature illustrated by case reports. Clin Rheumatol 17:524–530
13. Singh G, Kumari N, Aggarwal A, Krishnani N, Misra R (2007) Prevalence of subclinical amyloidosis in ankylosing spondylitis. J Rheumatol 34:371–373
14. Lehtinen K (1993) Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. Ann Rheum Dis 52:174–176
15. Kobak S, Oksel F, Kabasakal Y, Doganavsargil E (2007) Ankylosing spondylitis-related secondary amyloidosis responded well to etanercept: a report of three patients. Clin Rheumatol 26:2191–2194