RHEUMATOLOGY

Original article

Is axial psoriatic arthritis distinct from ankylosing spondylitis with and without concomitant psoriasis?

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Abstract

Objective. The aim of this study was to compare patients with ankylosing spondylitis with psoriasis (ASP) and without psoriasis (AS), to axial PsA (axPsA) patients.

Methods. Two adult cohorts were recruited from the AS clinic: ASP and AS. These two cohorts were compared with two adult cohorts recruited from the PsA clinic: axPsA (radiographic sacroiliitis: \geq bilateral grade 2 or unilateral grade 3 or 4); and Peripheral PsA. All patients were followed prospectively according to the same protocol. The demographic, clinical and radiographic variables were compared. Adjusted means were used to account for varying intervals between visits. A logistic regression was performed and adjusted for follow-up duration.

Results. There were 477 axPsA patients, 826 peripheral PsA, 675 AS and 91 ASP patients included. AS patients were younger (P < 0.001), more male and HLA-B*27 positive (76%, 72% vs 64%, $P \le 0.001$, 82%, 75%, vs 19%, P = 0.001). They had more back pain at presentation (90%, 92% vs 19%, P = 0.001), worse axial disease activity scores (bath ankylosing spondylitis disease activity index: 4.1, 3.9 vs 3.5 P = 0.017), worse back metrology (bath ankylosing spondylitis metrology index: 2.9, 2.2 vs 1.8, P < 0.001), worse physician global assessments (2.4, 2.2 vs 2.1, P < 0.001), were treated more with biologics (29%, 21% vs 7%, P = 0.001) and had a higher grade of sacroiliitis (90%, 84% vs 51%, P < 0.001). Similar differences were detected in the comparison of ASP to axPsA and in a regression model.

Conclusion. AS patients, with or without psoriasis, seem to be different demographically, genetically, clinically and radiographically from axPsA patients. axPsA seems to be a distinct entity.

Key words: axial, psoriatic, arthritis, ankylosing, spondylitis

Rheumatology key messages

SCIENCE

- Axial psoriatic arthritis is different demographically compared with ankylosing spondylitis with and without psoriasis.
- Axial psoriatic arthritis is associated with worse peripheral arthritis and less back pain.
- Axial psoriatic arthritis and ankylosing spondylitis with psoriasis seem to be two different diseases.

Introduction

The term spondyloarthritis (SpA) encompasses a group of interrelated disorders that includes ankylosing spondylitis (AS) and PsA. These overlapping diseases share

¹Krembil Research Institute, Toronto Western Hospital, University Health Network, ²Institute of Medical Science, ³Division of Rheumatology, Department of Medicine, ⁴Department of Laboratory Medicine and Pathobiology, ⁵Department of Immunology, Medical Sciences Building, University of Toronto, Toronto and ⁶Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada

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Correspondence to: Dafna D. Gladman, Psoriatic Arthritis Program, Centre for Prognosis Studies in the Rheumatic Diseases, University Health Network, Toronto Western Hospital, 399 Bathurst Street, 1E411, Toronto, ON M5T 2S8, Canada. E-mail: dafna.gladman@utoronto.ca several typical features: association with HLA-B*27, inflammatory back pain, peripheral arthritis, enthesitis and dactylitis, as well as extra-articular features such as uveitis, psoriasis and inflammatory bowel disease. In 2011, the Assessment of Spondyloarthritis International Society (ASAS) introduced the concept of SpA being defined as either axial SpA or peripheral SpA [1]. Although the prototypical type of axial SpA remains AS, Moll and Wright recognized the presence of spinal disease as one of the patterns of PsA in their seminal paper from 1973 [2]. Because 10% of AS patients have concomitant psoriasis [3] and 25-70% of PsA patients have axial involvement [4, 5], the question arises whether AS with and without psoriasis and axial PsA are different phenotypes on the spectrum of the same disease or whether they are different diseases with overlapping features.

Several studies have compared AS patients to axial PsA patients [6-10]. Axial PsA seems to develop at an older age than AS and is less associated with HLA-B*27. Additionally, axial PsA emerges as less symptomatic than AS. However, both diseases have been reported to have similar levels of disease activity based on BASDAI (bath ankylosing spondylitis disease activity index), ASDAS (ankylosing spondylitis disease activity index score), HAQ and patient global assessment of axial disease activity. The comparisons published have several significant limitations: none have compared specifically axial PsA to AS with psoriasis. In contrast, a recent comparison from 2017 clustered these two groups in a combined group called psoriatic spondylitis and compared them to peripheral PsA (pPsA) and AS without psoriasis [6]. Another limitation is that all these previous studies have been cross-sectional in design, capturing and comparing patients at different stages of their disease.

The aim of this study was to compare two observational longitudinal PsA and AS cohorts, specifically AS with concomitant psoriasis. The comparison focused on the demographic, clinical and radiographic features of these cohorts at baseline and over time.

Methods

Patient population

A retrospective analysis was performed on two observational longitudinal cohorts, recruited from the adult Toronto Spondylitis Clinic and adult Toronto PsA Clinic. All patients in the clinic who are older than 18 years and who give their informed consent are included in these cohorts. Patients are entered into the PsA cohort if they have an inflammatory arthritis (peripheral or axial) in the presence of psoriasis [11]. Patients in the AS clinic are entered if they can be classified according to the modified New York AS criteria (mNY AS) [12].

Patient assessments

Patients from both clinics have been followed up prospectively according to the same standard protocol in which demographic, clinical (e.g. arthritic features and measures, presence of extra-articular manifestations and functional parameters), medication history, laboratory and imaging data are systematically recorded. The regular protocol visits are done every 6–12 months. The ASDAS is calculated [13].

Each clinic is supervised by two different staff rheumatologists. The SpA experts (Drs Inman and Haroon) follow the ASAS/EULAR and ACR/SPARTAN recommendations on the management of axial SpA [14, 15]. The reliability data of these readers regarding pelvic X-rays was found to be as follows: average intra-class correlation coefficients of 0.88 (95% CI 0.86, 0.91) and 0.89 (95% CI 0.87, 0.9) for grading right and left sacroiliac joints, respectively [16]. The radiographs of the AS patients were scored separately by two rheumatologists; if their interpretation was not identical, a third assessor determined the final interpretation. The PsA experts (Drs Gladman and Chandran) follow the GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis), EULAR and ACR treatment recommendations for PsA [17, 18]. Their reliability as measured by intra- and interrater intra-class correlation coefficients for grading sacroiliitis was found to be 0.81 and 0.67, respectively [19]. In the PsA clinic, radiographs were scored by consensus of at least two readers. Both the PsA experts and AS experts have had a formal SPARCC (Spondyloarthritis Research Consortium of Canada) training in axial metrology assessment and follow these guidelines.

For the current study, we identified consecutive patients entered in the database of these cohorts between 2003 and 2017 in the AS clinic and between 1973 and 2017 in the PsA clinic.

The AS cohort was divided into two groups: 'AS with psoriasis' (AS patients who were recorded to have psoriasis during their follow-up or had a history of psoriasis); and 'AS without psoriasis' (AS patients who were never reported to have psoriasis).

Ninety-nine percent of the patients in the PsA cohort fulfilled the CIASsification of Psoriatic ARthritis (CASPAR) criteria [20]. They were divided into two groups: 'Axial PsA' (patients who fulfil the radiographic arm of the mNY AS criteria (=at least bilateral sacroiliitis grade 2 or unilateral sacroiliitis grade 3 or 4)); and 'pPsA' (PsA patients with exclusively peripheral disease).

Patients without pelvic radiographs were not included in this study. The definition of axial disease was based upon the worst sacroiliac score the patient had ever fulfilled during the follow-up. Baseline visit was defined as the visit these definitions were met. In the AS and pPsA groups it was the first visit to the clinic, while in the axial PsA groups it was the visit of the first radiograph the patient had met the mNY AS radiographic criteria. The follow-up visits were defined as the visits after the visit with the defining radiograph. One visit per year per patient was included in the analysis, the first in each calendar year. Data of both databases are tracked on a webbased database. The study was approved by the Research Ethics Board of the University Health Network, Toronto.

Statistical analysis

Descriptive analyses were conducted on patient demographics, exposures, clinical characteristics, patient-reported outcomes and medication history for all patients in the four groups. Pair-wise comparisons were made between the AS with psoriasis group and axial PsA group. Categorical variables (e.g. sex, race, current or past smoking) were summarized using frequency counts and percentages. Continuous variables (e.g. age, clinical and disease measures) were summarized by the counts and means (s.p.). For the comparison of the four groups, ANOVA was used for continuous variables and Pearson χ^2 test for categorical variables. In the pairwise comparisons, *t* test was used for continuous variables, Wilcoxon rank test for non-normal continuous or discrete variables and Pearson χ^2 test for positive count variables and alllevel counts variables. For longitudinal analysis of variables that were expected to change over time, an adjusted mean (AM) was calculated [21]. The AM accounts for varying time intervals between visits, which is commonly seen in clinic settings. The AM of these variables is equivalent to the area under the curve of the value of the variable over time divided by the time interval [22]. In order to adjust for possible confounders, such as follow-up duration, a logistic regression was performed. When P < 0.05, the results were considered statistically significant. All analyses were performed using SAS version 9.3 from SAS Institute (Cary, NC, USA).

Results

Seven hundred and sixty-six patients were identified with AS, of whom 675 patients did not have any history of psoriasis. Ninety-one patients (12%) were reported to have concomitant psoriasis, 21 had psoriasis at their baseline visit, while 70 developed their psoriasis over their follow-up period.

One thousand three hundred and three patients were recruited from the PsA clinic, of whom 477 were identified as axial PsA, 61% had axial disease at their presentation, while the rest developed their axial disease over time. Eight hundred and twenty-six PsA patients were defined as the 'pPsA' group. The mean follow-up in the axial and pPsA groups was 12.6 and 6.7 years, respectively; in the AS groups with and without psoriasis, 5.4 and 3.5 years, respectively.

Seven hundred and sixty-six AS patients were included, of whom 91 had psoriasis, and 675 did not have concomitant psoriasis. Baseline demographic and genetic characteristics in these groups are depicted in Table 1. Patients with AS without psoriasis were younger at first visit, and both groups of AS patients were younger at diagnosis than patients with PsA, with or without axial disease (Table 1). There were more males among the AS group than either of the PsA groups. HLA-B*27 was more prevalent among patients with AS than those with axial PsA.

The clinical features in the AS and PsA patients are demonstrated in Table 2. Patients with PsA, with or without axial disease, had more actively inflamed and damaged joints, whereas patients with AS, with or without psoriasis, were more likely to have back pain, and a higher bath ankylosing spondylitis metrology index (BASMI) score at presentation. However, all patients had back pain during the entire follow-up. Enthesitis was most common in the pPsA group, similar prevalence of enthesitis was seen in the axial PsA and both AS groups. Dactylitis was diagnosed only in the PsA groups, not in the AS groups. Iritis was uncommon at presentation in both groups but more likely to occur among the AS patients. More of the AS patients were receiving biologic agents at the baseline visit, while more PsA patients were receiving conventional DMARDs.

The longitudinal analysis revealed that, over time, patients with PsA had more actively inflamed joints, whereas the AS patients had a higher BASMI. However, there was no difference in the ASDAS score over time, and the AM BASDAI score was also very similar. Patients in all four groups rated their disease activity similarly, while there was a slight difference in the physician assessment in favour of the AS group. Similar differences were also noted in pairwise comparisons of the axial PsA group to the AS with psoriasis group.

Milder grades of sacroiliitis on radiographs were noted among the patients with axial PsA patients compared with the two AS groups; 51% of patients with axial PsA had bilateral grade 2 sacroiliitis compared with only 14.6% in the AS groups, all the rest of the patients had a worse grade of sacroiliitis.

Table 3 presents the logistic regression comparing AS with psoriasis to axial PsA. Both univariate and multivariate analyses demonstrate that after adjusting for follow-up duration, sex, age, HLA*B27 status and treatment, AS with psoriasis is associated more with HLA*B27, a higher AM BASMI, worse sacroiliitis and more use of biologics, whereas axial PsA is associated with more peripheral arthritis.

Discussion

The main results of this study were that AS patients, with and without psoriasis, seemed to be different from axial PsA patients. AS patients were ~15 years younger at their first manifestation of arthritis and first presented to the clinic 7 years earlier. AS patients had a much higher male predominance and were four times more likely to be HLA-B*27 positive. AS patients had a worse axial disease compared with axial PsA, whereas axial PsA was associated with a worse peripheral arthritis. AS patients had more back pain at presentation, worse disease activity scores, worse back metrology, worse physician global assessments and were more likely to be treated with a biologic. They also had a worse grade of sacroiliitis on their radiographs. Even after adjusting for the demographic and HLA-B*27 differences, the axial and peripheral arthritis features remain significantly different. This has been previously reported in another setting using a different cohort of patients with AS. That study demonstrated that AS patients had an earlier onset of disease than patients with axial PsA, there were more males, and they had more severe disease [23].

In light of these demographic, genetic, clinical and radiographic differences, it seems reasonable to speculate that AS, with and without psoriasis, seems to be a different disease from axial PsA and that they are not merely two entities on the spectrum of the same disease.

Several similarities and differences exist between our study and a previous study published by Jadon *et al.* regarding the Bath cohort [6]. Their results suggest that psoriasis seems to be associated with a milder radiographic disease and does not seem to affect the axial disease clinically (metrology and disease activity wise). These contradictory results could be explained by the different study designs. Firstly, the Bath study was cross-sectional, they miss the important contribution of longitudinal assessment our study performed. Secondly, the patient groups in the Bath cohort were defined

TABLE 1 T	he comparison	of the baseline	demographic and	appatic characteristics	between the four groups
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	Ankylosing spondylitis		Psoriatic arthritis			
Variable	With psoriasis (<i>n</i> = 91)			Peripheral (n = 826)	<i>P</i> -value	
Age at visit, mean (s.p.)	40.4 (12.4)	38.2 (13.4)	45.9 (13.2)	45.1 (13.3)	<0.001	
Age of diagnosis, mean (s.p.)	28.7 (11.0)	30.4 (12.0)	35.6 (13.3)	39.3 (13.7)	< 0.001	
Age at start of any arthritis: peripheral or back pain, mean (s.p.)	21.3 (10.2)	22.9 (10.4)	34.4 (12.8)	37.5 (14.2)	<0.001	
Male, n (%)	69 (76)	489 (72)	303 (64)	414 (50)	< 0.001	
White Caucasian, n (%)	78 (86)	499 (74)	91 (19)	705 (85)	<0.001	
HLA-B*27, n (%)	75 (82)	509 (75)	91 (19)	77 (9)	<0.001	
Ever have smoked, n (%)	42 (46)	263 (39)	198 (42)	314 (38)	0.39	
Drinks alcohol on a daily/ social basis, n (%)	38 (42)	367 (54)	168 (35)	381 (46)	<0.001	
On disability/sick leave at presentation, n (%)	14 (15)	69 (10)	44 (9)	49 (6)	0.002	
College or above, <i>n</i> (%)	49 (54)	389 (58)	201 (42)	449 (54)	<0.001	

TABLE 2 The comparison of the baseline and longitudinal clinical characteristics between the four groups

	Ankylosing spondylitis		Psoriatic arthritis			
Variable	Psoriasis (n = 91)	No psoriasis (n = 675)	Axial (n = 477)	Peripheral (N = 826)	<i>P</i> -value	
At baseline						
Active joints (tender + swollen), mean (s.p.)	1.3 (3.1)	1.1 (3.5)	8.5 (10.1)	9.2 (9.9)	<0.001	
Damaged joints, mean (s.p.)	0.7 (4.6)	0.2 (1.3)	5.5 (9.9)	1.8 (5.0)	<0.001	
Joints after surgery, mean (s.D.)	0.1 (0.6)	0.1 (0.5)	0.3 (1.6)	0.1 (0.6)	0.44	
Presence of inflammatory or mechanical back pain, n (%)	82 (90)	618 (92)	100 (21)	253 (31)	<0.001	
ASDAS-ESR, mean (s.d.)	2.8 (1.3)	2.6 (1.1)	4.8 (3.0)	2.6 (1.1)	0.05	
Patient global assessment, mean (s.p.)	4.9 (3.0)	4.7 (2.8)	1.9 (1.7)	4.9 (2.5)	0.25	
BASMI, mean (s.d.)	3.1 (2.4)	2.3 (2.3)	1.9 (1.7)	1.2 (1.3)	<0.001	
Enthesitis, n (%)	12 (13)	75 (11)	68 (14)	150 (18)	0.001	
Dactylitis, n (%)	0	0	146 (31)	213 (26)	0.08	
Iritis, n (%)	2 (3)	9 (2)	2 (0)	0 (0)	<0.001	
Elevated ESR, n (%)	31 (34)	198 (29)	70 (15)	288 (35)	< 0.001	
Receiving biologics, n (%)	26 (29)	145 (21)	327 (69)	56 (7)	< 0.001	
Receiving NSAIDs, n (%)	47 (52)	340 (50)	216 (45)	435 (53)	0.04	
Receiving DMARDs, n (%)	12 (13)	84 (12)	5.2 (6.5)	232 (28)	< 0.001	
Over time, adjusted mean (s.p.)						
Total active joint	1.5 (3.5)	0.9 (2.2)	5.2 (6.5)	5.6 (6.6)	< 0.001	
BASMI	2.9 (2.2)	2.2 (2.1)	1.8 (1.4)	1.4 (1.2)	< 0.001	
ASDAS-ESR	2.3 (0.9)	2.2 (0.9)	2.2 (1.0)	2.1 (0.8)	0.58	
BASDAI	4.1 (2.0)	3.9 (2.1)	3.5 (2.2)	3.6 (2.0)	0.02	
Patient global assessment	4.3 (2.2)	4.1 (2.2)	2.1 (0.6)	3.9 (2.0)	0.34	
Physician global assessment	2.4 (0.9)	2.2 (0.8)	4.0 (2.3)	2.0 (0.7)	< 0.001	

ASDAS-ESR: ankylosing spondylitis disease activity score-erythrocyte sedimentation rate; BASDAI: bath ankylosing spondylitis disease activity index; BASMI: bath ankylosing spondylitis metrology index.

differently from our groups. In the Bath cohort, the researchers compared peripheral arthritis patients and AS without psoriasis patients to a third combined group of patients, which combined AS with psoriasis patients and axial PsA patients. They did not differentiate between axial PsA and AS with psoriasis. This mixture of patients surely affected their results. Thirdly, in the Bath cohort, axial PsA patients were defined differently, by mNY AS radiographic criteria and/or ≥ 1 marginal/paramarginal syndesmophytes of the cervical and/or lumbar spine. Thirty-three percent of their patients had syndesmophytes without sacroiliitis. We did not include the spine in the diagnosis of the axial disease in our study, we only addressed the sacroiliac joints, similar to the diagnosis of AS [12]. A TABLE 3 Logistic regression, outcome: ankylosing spondylitis with psoriasis compared with axial PsA (axial PsA reference group)

	Univariate			Multivariate			
Variable	OR	95% CI	<i>P</i> -value	OR	95% CI	<i>P</i> -value	
Age	0.98	0.97, 1	0.075	0.97	0.93, 1.01	0.16	
Sex	1.8	1.08, 3.01	0.025	1.25	0.39, 3.98	0.7	
HLA-B*27	16.37	8.89, 30.13	<0.0001	10.98	3.86, 30.85	< 0.0001	
Active arthritis	0.68	0.61, 0.76	<0.0001	0.75	0.64, 0.86	< 0.0001	
ASDAS-ESR, adjusted mean	1.1	0.83, 1.45	0.51				
BASMI, adjusted mean	1.41	1.21, 1.63	<0.0001	1.44	1.02, 2.03	0.04	
Sacroiliitis (grade 3, 4)	7.58	3.68, 15.59	<0.0001	3.24	1.10, 9.49	0.03	
Biologics/NSAIDS	1.24	0.77, 1	0.37	1.07	0.37, 3.07	0.9	
Duration of follow-up	0.88	0.85, 0.92	<0.0001	0.86	0.78, 0.96	0.005	

Adjusted variables: length of follow-up, age, sex, HLA-B*27, biologic/NSAIDS treatment. ASDAS-ESR: ankylosing spondylitis disease activity score-erythrocyte sedimentation rate; BASMI: bath ankylosing spondylitis metrology index; OR: odds ratio.

fourth important difference between the studies is the sample size; the Bath study was performed on 400 patients, while our study included 2069 patients.

Our study additionally found a weak correlation between back pain and radiographic disease in PsA patients. Despite the fact that the PsA patients had radiographic axial disease, only 21% reported concurrent back pain. This finding supports the relatively asymptomatic nature of axial disease in PsA found also in previous studies [4, 22]. Another possible explanation for the lack of back pain despite radiographic axial disease in PsA is that the radiographs were preformed after the active disease already subsided and therefore the radiographic changes actually represent damage rather than inflammation. MRI studies could clarify this. At presentation, as expected per definition, AS patients reported more back pain compared with the PsA groups; surprisingly, the pPsA group also reported more back pain compared with the axial PsA group. However, over time this difference was diminished because all patients reported back pain during their follow-up. Similar results were reported in the Bath study [6]. The high prevalence of back pain in patients without radiographic axial disease could reflect the high prevalence of non-specific back pain in the general population, especially in the ages of our cohort, or could reflect nonradiographic SpA, which was not assessed in this study.

Axial disease activity indices (ASDAS-erythrocyte sedimentation rate and BASDAI) did not differ in the axial PsA group compared with the pPsA group despite past studies that found these indices reliable in the assessment of axial inflammation in PsA patients with good to moderate discriminative ability and correlation with different constructs of disease activity [24-26]. The poor performance of these indices in this study might be due to possible underlining non-radiographic SpA. Similarly, the patient global assessment did not differ between groups, perhaps because this patient-reported outcome is not specific for axial inflammation and is affected by disease activity in other domains. Despite these possible explanations, these findings question the reliability of these indices in assessing axial inflammation in PsA. Specific disease activity indices for axial inflammation in PsA, which will be able to assess the axial component of the disease independently from activity in other disease domains, are necessary.

This study has several strengths: it is a retrospective analysis of two large cohorts followed prospectively for a prolonged period using an identical protocol that gathered extensive demographic, genetic, radiographic and longitudinal clinical data at regular intervals. The longitudinal data provide information regarding the disease course, and this is especially important when comparing two diseases that change over time. The study was performed in one centre by a small number of dedicated, highly trained rheumatologists who have a special interest in SpA and PsA and have had similar training.

A limitation of this study is the case definition. Patients with significant back symptoms are more likely to be referred to the AS clinic, while patients with more prominent peripheral symptoms are more likely to be referred to the PsA clinic. Additionally, the patients in the AS groups were required to have back pain or limitation in spinal range of motion in order to be included in this study, while the patients in the axial PsA group could be asymptomatic. Because asymptomatic AS patients are rarely diagnosed and therefore are unlikely to present to the clinic, the severe cases of AS might have been compared with possibly milder cases of axial PsA. Despite these limitations, our results provide significant insights because the typical PsA patient was compared with the typical AS patient followed in these clinics. Both patient populations were assessed according to the same protocol, which included detailed history for both peripheral and axial disease as well as comorbidities, including psoriasis and nail lesions. The directors of the clinics trained the physicians working in the clinic in the metrology, and the data have been collected prospectively. Another limitation is that the study was performed in a tertiary centre,

perhaps missing the milder cases of disease. Mild cases, however, are present in the cohort, which might improve the generalizability of this study to primary rheumatology clinics.

The radiographic data regarding spinal disease are limited in this cohort. The mSASSS score is missing for many patients, so only the differences in the sacroiliitis scores were assessed. However, BASMI scores were available and they can serve as surrogates for mSASSS scores [22, 27-29]. In the AS group, information regarding PASI (psoriasis area and severity index) score, nail disease and radiographic assessment of peripheral joints is missing, so the severity of psoriasis and radiographically damaged joints cannot be compared between groups. However, information regarding clinically damaged joints was included in the analysis.

Additionally, an attrition bias is recognized. Milder patients are more likely to be 'lost to follow-up', leaving the more severe patients in the cohort, affecting the variables that change over time. However, this bias applies to both cohorts equally and might have not affected the comparison substantially.

In conclusion, our study suggests that axial PsA and AS with psoriasis seem to be two different diseases with different genetics, demographics and disease expression.

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