Demographic and clinical differences between ankylosing spondylitis and non-radiographic axial spondyloarthritis: results from a multicentre retrospective study in the Lazio region of Italy

M.S. Chimenti[1], P. Conigliaro[1], L. Navarini[2], F.M. Martina[3], G. Peluso[4], D. Birra[4], P. Sessa[5], M. Anzidei[6], P. Scolieri[7], V. Bruzzese[7], G. Santoboni[8], P. Cardello[9], E. Gremese[4], A. Afeltra[2], G. Valesini[5], G.D. Sebastiani[10], R. Perricone[1], R. Scrivo[5]

[1]Rheumatology, Allergology and Clinical Immunology, University of Rome Tor Vergata, Rome; [2]Unit of Allergology, Immunology and Rheumatology, Dept. of Medicine, Università Campus Bio-Medico di Roma; [3]Unità di Diagnostica per Immagini and Dip. di Medicina, Università Campus Bio-Medico di Roma; [4]Istituto di Reumatologia e Scienze Affini Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli, Presidio Columbus, Rome; [5]Reumatologia, Dip. di Medicina Interna e Specialità Mediche, Sapienza Università di Roma; [6]Radiologia, Dip. di Scienze Radiologiche Oncologiche ed Anatomopatologiche, Università Sapienza di Roma; [7]UOC Medicina Interna e Reumatologia, Ospedale Nuovo Regina Margherita, Rome; [8]UOC Medicina Generale Polo, [9]UOC Radiologia Diagnostica ed Interventistica, Ospedale Belcolle Viterbo; [10]UO Reumatologia, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy.

Abstract

Objective

Axial spondyloarthritides (axSpA) are a group of disorders that share similar pathogenetic mechanisms and clinical picture. The aim of this retrospective multicentric study was to evaluate demographic and clinical differences between ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA) patients.

Methods

Patients from 7 rheumatological centres in the Lazio region of Italy were included from January 1st, 2010 to April 1st, 2018, if they had undergone pelvic and/or spine radiographs or magnetic resonance imaging (MRI). Images were evaluated by one experienced radiologist in each centre who already had the clinical suspicion of axSpA. Clinical and therapeutic data were collected at the last observation visit. Categorical variables were presented with percentages and analysed by Chi squared test. Continuous variables were expressed as mean ± standard deviation and compared using the parametric unpaired t-test or the non-parametric Mann-Whitney U-test, when appropriate. p-values <0.05 were considered significant.

Results

210 axSpA patients were included: 65.2% with AS and 34.7% with nr-axSpA. When comparing the two groups, AS patients had longer disease duration, were older, were more frequently males, had a greater diagnostic delay and a higher body mass index than the nr-axSpA patients (p<0.0001, p<0.0001, p=0.003 p=0.007, and p=0.04, respectively). The peripheral joints of the nr-axSpA patients were more frequently involved, had higher frequency of inflammatory bowel disease, higher C-reactive protein levels and lower frequency of HLA-B27 positivity (p=0.005, p=0.007, p=0.01, and p=0.01, respectively). TNF inhibitors were used in 87.8% patients with AS and 78.3% with nr-axSpA (p=0.04). More fat metaplasia was observed on MRI in the nr-axSpA group than in the AS group at sacroiliac joints (p=0.003), and more backfills were detected in the AS group on spine-MRI (p=0.003). Spine-bone marrow oedema was more prevalent in AS than in nr-axSpA (p=0.04), and more sclerosis and backfill were found in AS (p=0.003 and p=0.01, respectively).

Conclusion

In clinical practice, distinctive features in AS and nr-axSpA patients emerged. Imaging is crucial in guiding the choice of treatment in order to control disease activity and inflammation.

Key words

axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, magnetic resonance imaging

Maria Sole Chimenti, MD, PhD, MSc
Paola Conigliaro, MD, PhD
Luca Navarini, MD
Francesca Maria Martina, MD
Giusy Peluso, MD
Domenico Birra, MD
Paola Sessa, MD
Michele Anzidei, MD
Palma Scolieri, MD
Vincenzo Bruzzese, MD
Gianluca Santoboni, MD
Paolo Cardello, MD
Elisa Gremese, MD, PhD, Prof.
Antonella Afeltra, MD, Prof.
Guido Valesini, MD, PhD, Prof.
Gian Domenico Sebastiani, MD, PhD, Prof.
Roberto Perricone, MD, Prof.
Rossana Scrivo, MD, PhD

Please address correspondence to:
Dr Maria Sole Chimenti,
Department of Rheumatology,
University of Rome Tor Vergata,
Viale Oxford 81,
00133 Roma, Italy.
E-mail: maria.sole.chimenti@uniroma2.it

Received on December 27, 2018; accepted in revised form on April 1, 2019.

G.D. Sebastiani ORCID iD: 0000-0003-2969-6649

Competing interests: R. Scrivo has received fees and/or speaker honoraria from Abbvie, BMS, Celgene, Janssen, MSD, Novartis and UCB.
The other co-authors have declared no competing interests.

Introduction

Spondyloarthritides (SpA) are a group of disorders sharing a genetic background and similar pathogenetic mechanisms and clinical picture. They are characterised by both inflammation and structural damage (1). In 2009 the Assessment of SpondyloArthritis international Society (ASAS) introduced the term "axial spondyloarthritis" (axSpA) to label patients with SpA and predominant involvement of the axial skeleton (2). The term axSpA comprises patients who fulfil the modified New York (mNY) criteria for ankylosing spondylitis (AS) (3), as well as those affected by non-radiographic axSpA (nr-axSpA), who can be identified by the presence of the typical clinical features of SpA combined with either active sacroiliitis seen on the magnetic resonance imaging (MRI) scan (imaging arm) or HLA-B27 positivity (clinical arm) (4). Hence, the ASAS classification criteria allow detecting patients in the non-radiographic stage of the disease at a much earlier time with respect to AS patients. This is due to the fact that the mNY criteria are met in the presence of radiographic sacroiliitis, yet patients with AS often have symptoms for several years before structural changes of the sacroiliac joints can be detected (5). Despite this, the delay between symptom onset and diagnosis in axSpA is estimated to still be more than 6 years (6). The main reason for such a delay is probably the late referral of patients with back pain to a rheumatologist by general practitioners and other physicians (7). Indeed, chronic back pain is highly prevalent in the general population, but it is estimated that only about 5% of these subjects have axSpA (8), often in the lack of specific physical, laboratory or imaging tests. Furthermore, patients themselves may seek care from physicians other than rheumatologists, and this also may result in a diagnostic delay. To overcome these difficulties, a first set of recommendations for referral of patients suspected of having axSpA by non-rheumatologists was developed with the intent to improve early diagnosis of axSpA (7). In the same vein of providing the optimal care for patients, a taskforce of experts developed evidence-based recommendations for the use of imaging in the diagnosis and monitoring activity and structural damage of SpA (9).

In this retrospective multicentric study, we aimed to identify the demographic, clinical, and therapeutical differences between AS and nr-axSpA patients. Also, imaging findings, including the prevalence of acute and chronic lesions at sacroiliac joints (SIJs) and spine are described.

Patients and methods

This is a retrospective study conducted on consecutive outpatients classified as affected by AS according to the mNY criteria (3) or nr-axSpA according to the ASAS criteria (4) attending the Rheumatology Units of 7 tertiary referral centres in the Lazio region of Italy between January 1st, 2010 and April 1st, 2018. Centres were selected on the presence of an experienced radiologist for the musculoskeletal assessment. Patients were included if they were aged >18 years, had a diagnosis of axSpA >6 months, and had undergone pelvic and/or spine radiographs or MRI.

At recruitment, data on demographics, current or past history of smoking, body mass index (BMI), diagnosis (AS or nr-axSpA), age at disease onset, age at diagnosis of axSpA, presence at any time of peripheral arthritis, dactylitis, enthesitis and of extra-articular manifestations (*i.e.* uveitis, inflammatory bowel disease (IBD), psoriasis), human leukocyte antigen (HLA)-B27 positivity, comorbidities, family history of immune-mediated inflammatory disease (IMID) were obtained and collected on a standardised electronic form. The disease activity was measured by the Bath AS disease activity index (BASDAI) (10) and the AS disease activity score (ASDAS) with C-reactive protein (CRP) (11). The Bath AS functional index (BASFI) to measure functional ability was also registered when available (12).

In order to determine the diagnostic delay, age at disease onset was defined as the date of the first appearance of SpA-related symptoms, including inflammatory back pain (IBP) defined according to the ASAS criteria (4), peripheral arthritis, enthesitis and dactylitis. Diagnostic delay was defined as the du-

ration (years) between symptom onset and time of diagnosis (13).
Details were also recorded concerning current anti-rheumatic treatments, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and biological DMARDs (bDMARDs), in particular TNF inhibitors (TNFi).

Imaging assessment
Experienced musculoskeletal radiologists (one for each centre) aware of the clinical suspicion of axSpA evaluated and described the radiographic and MRI imaging for both sacroiliac joints (SIJs) and spine. Based on the mNY criteria, radiographic sacroiliitis was defined as bilateral grade ≥2 or unilateral grade ≥3 (3). At the spine level, Romanus lesions, "shiny corners", spondylodiskitis and syndesmophytes were assessed (13). T1-weighted fast spin echo and short τ inversion recovery 1–1.5 tesla MRI of the SIJs (SIJs-MRI) and the whole spine (spine-MRI) were performed. SIJs-MRI images were considered positive according to the ASAS definition (*i.e.* presence of bone marrow oedema (BME) lesions highly suggestive of SpA with ≥1 BME lesion on ≥2 consecutive slices or several BME lesions visible on a single slice (14). Apart from BME, inflammatory changes detected by MRI included capsulitis, synovitis and enthesitis; structural lesions were also assessed, such as bone erosions, new bone formation, sclerosis and fat infiltration. The MRI inflammation in the spine was defined according to the ASAS/OMERACT criteria (15).
The study was approved by the local ethics committees of the institutions involved. Informed consent was obtained from all the patients before they were included in the study, which was conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with good clinical practice guidelines.

Statistical analysis
To test normality of data sets, the D'Agostino and Pearson omnibus test was used. Normally distributed variables were summarised using mean and standard deviation (SD). Categorical variables were presented with absolute frequencies and percentages. Continuous variables were compared using the parametric unpaired *t*-test or the non-parametric Mann-Whitney U-test when appropriate. Univariate comparisons between nominal variables were performed by Chi squared test. *p*-values <0.05 were considered significant. All statistical analyses were performed using GraphPad Prism v. 6 (GraphPad Software, Inc., San Diego, CA, USA).

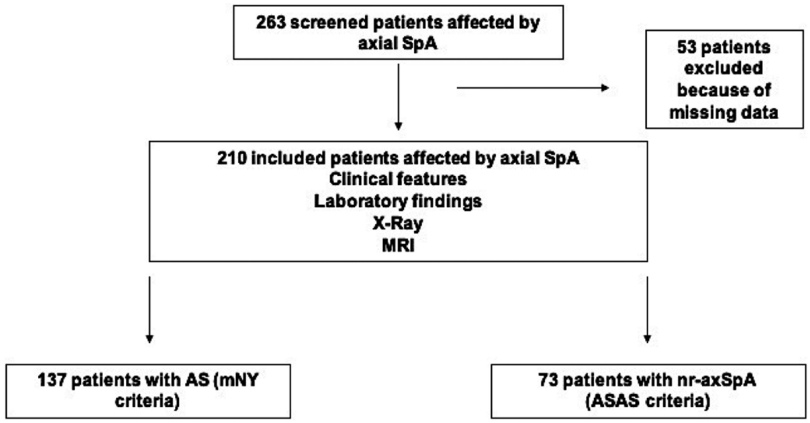

Fig. 1. Study flow-chart.
AS: ankylosing spondylitis; nrAxSpA: non-radiographic axial spondyloarthritis; MRI: magnetic resonance imaging; ASAS: Assessment of SpondyloArthritis international Society; mNY: modified New York.

Results

A total of 263 axSpA patients were considered for the study. However, 53 were excluded because of missing clinical and/or laboratory and/or imaging data (Fig. 1). Demographic and clinical characteristics of the patients enrolled are summarised in Table I.

Comparison of demographic and clinical characteristics: AS vs nr-axSpA patients
A total of 137 patients (65.2%) satisfied the mNY criteria and were classified as having AS and 73 (34.7%) satisfied the ASAS criteria for nr-axSpA. Mean (SD) axSpA disease duration was 7.5±8.9 years; when comparing the two groups, patients affected by AS had a higher disease duration than patients with nr-ax-SpA ($p<0.0001$) (Fig. 2A). A statistically significant difference was obtained comparing age at the disease onset: patients affected by AS were older than patients affected by nr-axSpA ($p<0.0001$) (Fig. 2B). Likewise, there was a higher prevalence of males among the AS patients ($p=0.003$) with respect to those affected by nr-axSpA (Fig. 2C). Patients with AS had also a significantly higher BMI (Fig. 2D) compared to patients with nr-axSpA ($p=0.04$).
With respect to clinical manifestations, patients affected by nr-axSpA had a more prevalent peripheral involvement ($p=0.005$) and a higher frequency of IBD ($p=0.007$). Concerning laboratory parameters, patients affected by nr-axSpA had higher CRP levels with respect to those with AS ($p=0.01$) (Fig. 3). On the contrary, AS patients presented higher positivity for HLA-B27 compared to nr-axSpA ($p=0.01$). Neither differences in the clinimetric indices (BASDAI, ASDAS-CRP, and BASFI) nor in smoking habits, family history of IMID, presence of enthesitis, uveitis, psoriasis, and comorbidities were observed.

Evaluation of diagnostic delay: AS vs nr-axSpA patients
The diagnostic delay was calculated for all patients enrolled. A significant difference emerged between the two groups: patients affected by AS had a longer diagnostic delay than patients affected by nr-axSpA ($p=0.007$) (Fig. 4).

Differences concerning treatment approach
Patients treated with TNFi were a total of 169 (80.5%), of whom 115 (83.9%) had AS and 54 (74%) nr-axSpA ($p=0.04$). No differences were observed concerning NSAIDs, glucocorticoid or csDMARD use.

Table I. Differences in the demographic and clinical characteristics of the study population.

	Total axSpA (n=210)	nr-AxSpA (n=73)	AS (n=137)	*p*-value
Age at onset, years	46.35 ± 14.63	39.83 ± 1.49	49.63 ± 1.25	<0.0001
Male, n (%)	118 (56.2)	31 (42.4)	87 (60.5)	0.003
Disease duration, years	8.99 ± 8.2	4.25 ± 0.42	10.61 ± 0.98	<0.0001
BMI	24.14 ± 5.84	25.3 ± 0.89	22.17 ± 1.36	0.04
HLA-B27, n (%)	79 (37.6)	19 (26)	60 (43.8)	0.01
Smoking, n (%)	38 (18.1)	12 (16.4)	26 (19)	NS
Diagnostic delay, years	4.83 ± 7.08	3.04 ± 0.44	5.91 ± 0.79	0.007
Peripheral involvement, n (%)	94 (44.8)	42 (57.5)	52 (37.9)	0.005
Enthesitis, n (%)	54 (25.7)	32 (43.8)	22 (16.1)	NS
Dactylitis, n (%)	23 (10.9)	9 (12.3)	14 (10.2)	NS
Uveitis, n (%)	30 (14.3)	9 (12.3)	21 (15.3)	NS
Psoriasis, n (%)	23 (10.9)	9 (12.3)	14 (10.2)	NS
IBD, n (%)	73 (34.8)	34 (46.6)	39 (28.5)	0.007
Comorbidities, n (%)	95 (45.2)	32 (43.8)	63 (46)	NS
IMID Family history, n (%)	46 (21.9)	16 (21.9)	30 (21.9)	NS
CRP (mg/dL)	1.76 ± 6.03	2.34 ± 0.73	0.92 ± 0.13	0.01
ASDAS-CRP	2.51 ± 1.07	2.5 ±1.2	2.5 ± 0.9	NS
BASDAI	4.22 ± 2.53	4.4 ± 2.6	4.1 ± 2.4	NS
BASFI	4.3 ± 2.9	4.3 ± 2.6	4.5 ± 3	NS
NSAIDs, n (%)	151 (71.9)	52 (71.2)	99 (72.3)	NS
Glucocorticoids, n (%)	94 (44.7)	37 (50.7)	57 (41.6)	NS
csDMARDs, n (%)	117 (55.7)	41 (56.2)	76 (55.5)	NS
TNFi, n (%)	169 (80.5)	54 (74)	115 (83.9)	0.04

Data are expressed as mean/SD unless otherwise specified.
BMI: body mass index; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; IMID: immune-mediated inflammatory disease; CRP: C-reactive protein; ASDAS-CRP: ankylosing spondylitis disease activity score-CRP; TNFi: tumour necrosis factor-inhibitors; AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; nr-axSpA: non-radiographic axial SpA; NSAIDs: non-steroidal anti-inflammatory drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IBD: inflammatory bowel disease.

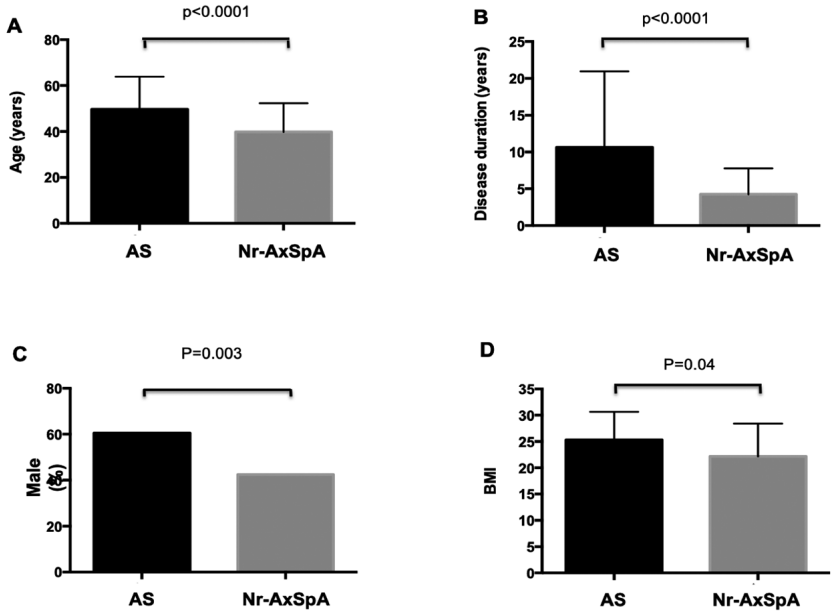

Fig. 2. Differences in demographic and clinical characteristics between ankylosing spondylitis and non-radiographic axial spondyloarthritis patients. **A:** differences in age (years)**; B** differences in disease duration (years)**; C:** differences in BMI (values)**.**
AS: ankylosing spondylitis; nrAxSpA: non-radiographic axial spondyloarthritis; BMI: body mass index.

Imaging assessment

Conventional radiography of the SIJs had been made in 210 patients (100%), and in 74 cases (35.2%) a diagnosis of sacroiliitis was made. Spine radiography was performed in 156 patients (74.3%): syndesmophytes were detected in 66 (31.4%). SIJs-MRI was available for 146 patients (69.5%), showing all of the following: BME (n=80; 67.8%), sclerosis (n=58; 49.1%), erosions (n=26; 22%), fat infiltration (n=15; 12.7%), new bone formation (n=10; 8.8%). Spine-MRI was available in 56 cases (26.7%): both BME and sclerosis were observed in 15 patients (35.7%), erosions in 3 (7.1%), fat infiltration in 8 (19%), new bone formation in 10 (23.8%), spondylodiscitis in 3 (7.1%). MRI findings are summarised in Table II.

Comparing the two study populations, more fat metaplasia was observed in the nr-axSpA group with respect to the AS group at the SIJs-MRI (p=0.003). On the contrary, more backfills were detected in the AS group compared to the nr-axSpA patients at the spine-MRI (p=0.003).

No differences concerning BME or chronic lesions including sclerosis and erosions were observed at SIJs-MRI.

When evaluating spine-MRI, BME was more prevalent in patients affected by AS than in those with nr-axSpA (p=0.04) while, concerning chronic lesions, a higher prevalence of sclerosis and backfill was found in AS patients (p=0.003 and p=0.01, respectively).

Discussion

Since its establishment in the 1970s, the disease concept of SpA has seen major developments with respect to identification and classification of the disease, measurement and prediction of outcome, and treatment options (1). SpA represent a challenge for both rheumatologist and radiologist, especially in its axial form. Wide range of difference estimates, across geographic regions, are present, classically related to the presence of HLA–B27. In particular, the prevalence of SpA is higher in studies from North America (1.35%; 95% CI 0.44–2.79; n=1 study) and Europe (0.54%; 95% CI 0.36–0.78) compared with South Asia (0.22%; 95% CI 0.01–0.66) and South-East Asia (0.20%; 95% CI 0.00–0.66) (17). In Italy, AS has an estimated prevalence of 0.37% (18). The absence of population-based prevalence estimates for nr-axSpA may be due to the historical lack of classification criteria for this population (19); also in our country the

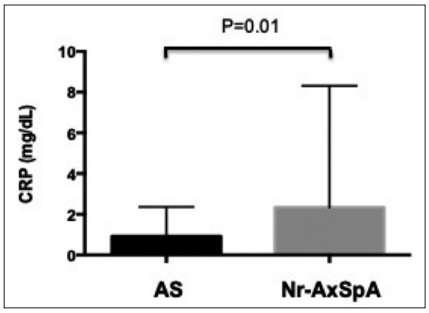

Fig. 3. Differences in CRP levels between ankylosing spondylitis and non-radiographic axial spondyloarthritis patients.
CRP (mg/dl): C-reactive protein.

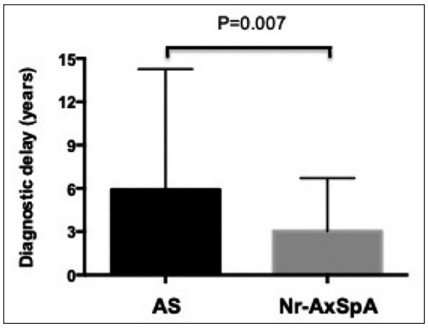

Fig. 4. Evaluation of diagnostic delay (years).
AS: ankylosing spondylitis; nr-axSpA: non-radiographic axial spondyloarthritis.

Table II. Differences in imaging assessment of the study population.

	Total axSpA (n=210)	Nr-axSpA (n=73)	AS (n=137)	*p*-value
SIJs MRI-				
BME, n (%)	111 (52.8)	41 (56.2)	70 (51.1)	NS
Sclerosis, n (%)	81 (38.6)	25 (34.2)	56 (40.9)	NS
Erosions, n (%)	35 (16.7)	10 (13.7)	25 (18.2)	NS
Fat metaplasia, n (%)	35 (16.7)	20 (27.4)	15 (10.9)	0.002
Backfills, n (%)	14 (6.7)	0	14 (10.2)	0.003
Spine MRI				
BME, n (%)	17 (8.1)	2 (2.7)	15 (10.9)	0.04
Sclerosis, n (%)	16 (7.6)	0	16 (11.7)	0.003
Erosions, n (%)	13 (6.2)	1 (1.4)	12 (8.7)	NS
Fat metaplasia, n (%)	5 (2.3)	0	5 (3.6)	NS
Backfills, n (%)	11 (5.2)	0 (0)	11 (8)	0.01

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; nrAxSpA: non-radiographic axial SpA; BME: bone marrow oedema; MRI: magnetic resonance imaging; SIJs: sacroiliac joints.

prevalence concerning nr-axSpA is still missing. Our study, based in the centre of Italy (Lazio region), evaluated the characteristics of patients affected by axial SpA: a more prevalent diagnosis of AS with a longer disease duration emerged compared to nr-axSpA. These data support the concept that AS may be considered as the "next step" of nr-axSpA and is linked to more disability and pain, as well as structural lesions that are associated with a longer disease duration (2, 4). Patients affected by AS were also older, with higher prevalence of male sex, HLA-B27 positivity, and higher BMI than patients affected by nr-axSpA, confirming data in the literature. However, while the higher prevalence of AS in males may in part be an artefact induced by deficits in the diagnosis of AS in females (20), nr-axSpA was more common in female than in male subjects, indicating that females develop structural changes later or less frequently than males (21). We detected a higher BMI in AS patients than in nr-axSpA ones, supporting the hypothesis that a major amount of adipose tissue, which is considered a dynamic endocrine organ (22), is associated with an increased production of several proinflammatory cytokines and acute phase reactants, such as CRP, (23) and with a more aggressive radiographic progression (24). Indeed, it has been demonstrated that the majority of AS patients is overweight, and overweight patients have a greater burden of symptoms (25). Overweight may also limit physical activity, which is mandatory to prevent bone damage in SpA patients. Interestingly, data from the literature show that SpA, during its course, tends to associate with the development of some comorbidities (26). In our study, a higher prevalence of peripheral involvement and IBD was observed in nr-axSpA than in AS patients, as well as higher levels of CRP. The presence of peripheral arthritis and gastro-intestinal comorbidity may have enhanced the access of patients at the rheumatologic clinic (27). Indeed, it is well known that IBP is often misdiagnosed (28) and imaging may be helpful in differential diagnosis (29); on the contrary, the presence of inflammatory symptoms at peripheral joint levels may be easier diagnosed in daily clinical practice. This concept supports our result of a longer diagnostic delay in patients affected by AS than in nr-axSpA. Even with the use of ASAS criteria, a long diagnostic delay was observed in our patients affected by axSpA due to the absence of objectively detectable signs of the disease and a difficulty in discrimination between non-specific chronic low back pain and IBP. It has been widely demonstrated that an early axSpA diagnosis is mandatory in order to prevent structural damage and the progression to AS (30). Recent advances in the management of SpA have made diagnostic ascertainment crucial, since innovative alternatives therapies to NSAIDs have become available. Biological agents have proven their efficacy in axSpA, and in the early phase they are associated with substantial impairment of quality of life and high burden of disease (31). Recent evidence from REGISPONSERBIO (Spanish Register of Biological Therapy in Spondyloarthritides) suggests that, after the issue of the new classification criteria for SpA, biological therapy is being administered earlier than previously in SpA patients and in a higher proportion of patients with nr-axSpA (32). However, in our study, treatment with TNFi was more prevalent in AS patients, who displayed worse prognostic factors than nr-axSpA, as higher prevalence of HLAB-27 positivity, higher BMI and longer disease duration. In good clinical practice and in accordance to treatment recommendations, prognostic factors may indicate the use of TNFi (33). Concerning imaging, the interest in early axSpA was supported by the availability of advanced imaging modalities such as MRI to detect early sacroiliitis before radiographic structural damage appears (4). Here, we described the presence of chronic and acute lesions at SIJs and spine levels evaluated by a dedicated experienced radiologist. In our daily clinical practice, SIJs radio-

graphy and MRI were performed in the majority of the patients in accordance to the recommendations (9). Differences emerged between the two groups supporting the theory that patients may present acute lesions (BME, for example) and chronic lesions (as sclerosis) at the same time during the same evaluation, irrespective of the diagnosis of nr-axSpA or AS. These data underline the relevance of the use of MRI in order to evaluate inflammatory and structural lesions in axSpA during all the course of the disease and to evaluate the disease progression.

The main limits of our study are: i. the retrospective design that may limit the observation of inflammatory lesions at MRI; ii. the lack of a follow-up period.

Conclusions

This study highlighted distinctive features in patients with AS and nr-axSpA in daily clinical practice, in a real-life setting in the Lazio region in Italy. Several differences emerged in our study population concerning demographic and clinical characteristics and treatments approach. In good clinical practice, imaging is crucial in guiding the choice of treatment in order to control disease activity and inflammation. Further investigations on prospective analysis will be necessary in our daily clinical practice.

References

1. BAETEN D, BREBAN M, LORIES R, SCHETT G, SIEPER J: Are spondylarthritides related but distinct conditions or a single disease with a heterogeneous phenotype? *Arthritis Rheum* 2013; 65: 12-20.
2. RUDWALEIT M, LANDEWÉ R, VAN DER HEIJDE D *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis. Part I. Classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009; 68: 770-6.
3. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
4. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis. Part II. Validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
5. MAU W, ZEIDLER H, MAU R *et al*.: Clinical features and prognosis of patients with possible ankylosing spondylitis: results of a 10-year followup. *J Rheumatol* 1988; 15: 1109-14.
6. JOVANÍ V, BLASCO-BLASCO M, RUIZ-CANTERO MT, PASCUAL E: Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and metaanalysis. *J Rheumatol* 2017; 44: 174-83.
7. PODDUBNYY D, VAN TUBERGEN A, LANDEWÉ R, SIEPER J, VAN DER HEIJDE D; ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY (ASAS): Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. *Ann Rheum Dis* 2015; 74: 1483-7.
8. UNDERWOOD MR, DAWES P: Inflammatory back pain in primary care. *Br J Rheumatol* 1995; 34: 1074-7.
9. MANDL P, NAVARRO-COMPÁN V, TERSLEV L *et al*.; EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR): EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis* 2015; 74: 1327-39.
10. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
11. DOUGADOS M, GUEGUEN A, NAKACHE JP, NGUYEN M, MERY C, AMOR B: Evaluation of a functional index and an articular index in ankylosing spondylitis. *J Rheumatol* 1988; 15: 302-7.
12. CALIN A, GARRETT S, WHITELOCK H *et al*.: A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994; 21: 2281-5.
13. FELDTKELLER E, ERLENDSSON J: Definition of disease duration in ankylosing spondylitis. *Rheumatol Int* 2008; 28: 693-6.
14. HERMANN KG, ALTHOFF CE, SCHNEIDER U *et al*.: Spinal changes in patients with spondyloarthritis: comparison of MR imaging and radiographic appearances. *Radiographics* 2005; 25: 559-69.
15. LAMBERT RG, BAKKER PA, VAN DER HEIJDE D *et al*.: Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016; 75: 1958-63.
16. HERMANN KG, BARALIAKOS X, VAN DER HEIJDE DM *et al*.; ASSESSMENT IN SPONDYLOARTHRITIS INTERNATIONAL SOCIETY (ASAS): Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Ann Rheum Dis* 2012; 71: 1278-88.
17. STOLWIJK C, VAN ONNA M, BOONEN A, VAN TUBERGEN A: Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. *Arthritis Care Res* (Hoboken). 2016; 68: 1320-31.
18. D'ANGELO S, PADULA A, NIGRO A *et al*.: Italian evidence-based recommendations for the management of ankylosing spondylitis: the 3E Initiative in Rheumatology. *Clin Exp Rheumatol* 2008; 26: 1005-11.
19. BOHN R, COONEY M, DEODHAR A, CURTIS JR, GOLEMBESKY A: Incidence and prevalence of axial spondyloarthritis: methodologic challenges and gaps in the literature. *Clin Exp Rheumatol* 2018; 36: 263-74.
20. GRAN JT, HUSBY G, HORDVIK M: Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromso, northern Norway. *Ann Rheum Dis* 1985; 44: 359-67.
21. LUBRANO E, PERROTTA FM, MANARA M *et al*.: The sex influence on response to tumor necrosis factor-α inhibitors and remission in axial spondyloarthritis. *J Rheumatol* 2018; 45: 195-201.
22. GREMESE E, BERNARDI S, BONAZZA S *et al*.: Body weight, gender and response to TNF-α blockers in axial spondyloarthritis. *Rheumatology* (Oxford) 2014; 53: 875-81.
23. IBÁÑEZ VODNIZZA SE, NURMOHAMED MT, VISMAN IM *et al*.: Fat mass lowers the response to tumor necrosis factor-α blockers in patients with ankylosing spondylitis. *J Rheumatol* 2017; 44: 1355-61.
24. MAAS F, SPOORENBERG A, BROUWER E *et al*.: Spinal radiographic progression in patients with ankylosing spondylitis treated with TNF-α blocking therapy: a prospective longitudinal observational cohort study. *PLoS One* 2015; 10: e0122693.
25. DURCAN L, WILSON F, CONWAY R, CUNNANE G, O'SHEA FD: Increased body mass index in ankylosing spondylitis is associated with greater burden of symptoms and poor perceptions of the benefits of exercise. *J Rheumatol* 2012; 39: 2310-14.
26. TERENZI R, MONTI S, TESEI G, CARLI L: One year in review 2017: spondyloarthritis. *Clin Exp Rheumatol* 2018; 36: 1-14.
27. CONIGLIARO P, CHIMENTI MS, ASCOLANI M *et al*.: Impact of a multidisciplinary approach in enteropathic spondyloarthritis patients. *Autoimmun Rev* 2016; 15: 184-90.
28. TANT L, DELMOTTE N, VAN DEN ENDEN M, GANGJI V, MIELANTS H: High prevalence of undiagnosed axial spondyloarthritis in patients with chronic low back pain consulting non-rheumatologist specialists in Belgium: SUSPECT Study. *Rheumatol Ther* 2017;4:121-32.
29. BRAUN J, BARALIAKOS X, BUEHRING B, KILTZ U, FRUTH M: Imaging of axialspondyloarthritis. New aspects and differential diagnoses. *Clin Exp Rheumatol* 2018; 36: 35-42.
30. HAMMOUDEH M, ABDULAZIZ S, ALOSAIMI H *et al*.: Challenges of diagnosis and management of axial spondyloarthritis in North Africa and the Middle East: An expert consensus. *J Int Med Res* 2016; 44: 216-30.
31. ONUORA S: Spondyloarthritis: Predictive factors of anti-TNF efficacy. *Nat Rev Rheumatol* 2017; 13: 632.
32. MORENO M, GRATACÓS J, NAVARRO-COMPÁN V *et al*.; and the Regisponserbio group. Should over-treatment of axial spondyloarthritis with biologics remain a concern afterthe issue of the new ASAS criteria? Data from REGISPONSERBIO (Spanish Register of Biological Therapy in Spondyloarthritides). *Clin Exp Rheumatol* 2018; 36: 1038-42.
33. FAVALLI EG, BECCIOLINI A, CAPORALI R *et al*.; GISEA STUDY GROUP: The profiling of axial spondyloarthritis patient candidate to a biologic therapy: Consensus from a Delphi-panel of Italian experts. *Autoimmun Rev* 2018; 17: 1251-8.