Original article

Systemic auto-inflammatory manifestations in patients with spondyloarthritis

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ABSTRACT

Objectives. – (1) characterizing a group of spondyloarthritis (SpA) patients with systemic auto-inflammatory symptoms (S-SpA); (2) comparing SpA features with and without auto-inflammatory symptoms; (3) comparing the auto-inflammatory features of S-SpA and Still's disease (SD).

Methods. – Retrospective observational study. Clinical data of adult and pediatric patients with S-SpA, SD or SpA were collected retrospectively and analyzed.

Results. – Forty-one subjects with S-SpA, 39 with SD and 42 with SpA were enrolled. The median latency between systemic and articular manifestations in S-SpA was 4.4 (IQR: 7.2) years. S-SpA and SpA had similar frequency of peripheral arthritis and enthesitis (N.S.), while tenosynovitis was more frequent ($P = 0.01$) and uveitis less frequent ($P < 0.01$) in S-SpA. MRI showed signs of sacroiliac inflammation and damage in both S-SpA and SpA equally (N.S.). S-SpA patients had less corner inflammatory lesions ($P < 0.05$) and inflammation at the facet joints ($P < 0.01$), more interspinous enthesitis ($P = 0.01$) and inter-apophyseal capsulitis ($P < 0.01$). Compared to SD, S-SpA patients had lower-grade fever ($P < 0.01$), less rash ($P < 0.01$) and weight loss ($P < 0.05$), but more pharyngitis ($P < 0.01$), gastrointestinal symptoms ($P < 0.01$) and chest pain ($P < 0.05$). ESR, CRP, WBC, ANC, LDH tested higher in SD ($P < 0.01$). Resolution of systemic symptoms was less frequent in S-SpA than SD on corticosteroid ($P < 0.01$) and methotrexate ($P < 0.05$) treatment. When considering all SD patients, a complete response to corticosteroids in the systemic phase significantly reduced the likelihood of developing SpA (OR = 0.06, coefficient −2.87 [CI: −5.0 to −0.8]).

Conclusions. – SpA should be actively investigated in patients with auto-inflammatory manifestations, including undifferentiated auto-inflammatory disease and SD.

1. Introduction

Spondyloarthritis (SpA) characterizes a heterogeneous group of immune-mediated disorders observed in both adult and pediatric populations. From a nosological standpoint, this group encompasses ankylosing spondylitis, enthesitis-related arthritis (ERA) and

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psoriatic categories of juvenile idiopathic arthritis (JIA), as well as psoriatic arthritis, reactive arthritis, enteropathic arthritis, and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. Notably, manifestations of SpA have also been identified in individuals with other inflammatory conditions, including familial Mediterranean fever (FMF), Behçet's disease, psoriasis, sarcoidosis, hidradenitis, and pyoderma gangrenosum [1–5]. These conditions collectively exhibit a continuum of dysregulation within both innate and adaptive immune responses, underpinned by a distinct genetic background. This genetic profile includes the involvement of major histocompatibility complex (MHC)-I genes, antigen processing genes *ERAP1* and *ERAP2*, and the interleukin (IL)-23 receptor gene, which play a crucial role in the presentation of MHC-I peptides [1,6].

In addition, monocyclic or recurrent fever has been described in association with SpA, potentially taking shape as a distinct form among undifferentiated auto-inflammatory diseases (USAID) [7–11]. In the largest cohort described, there was a long interval between the onset of recurrent fever and the diagnosis of SpA, and some patients exhibited signs of joint damage and renal amyloidosis, indicating prolonged chronic inflammation [7]. Interestingly, instances of simultaneous diagnosis of SpA and Still's disease (SD) in the same patient have also been documented, occurring in both children and adults [12–15]. These dual diagnoses were observed either concurrently at disease onset or with a certain time lag. In the latter scenario, most patients showed ongoing disease activity when the second disease emerged, prompting the authors to postulate a potential phenotype shift between the two phenotypes [12].

In this study, we aimed to provide a thorough examination of the systemic inflammatory manifestations associated with SpA. Given the identified gaps in existing literature, we placed particular emphasis on two aspects: firstly, describing the articular and radiological features of SpA both in the presence and absence of systemic inflammatory signs, and secondly, comparing the systemic characteristics of SpA with those of SD.

2. Methods

2.1. Aims of the study

The primary aim of this study was to describe a cohort of patients with SpA and associated systemic inflammatory manifestations, including fever and potential organ-specific inflammation.

Secondary aims were (1) to identify potential differences in the articular and radiological features of SpA based on the presence or absence of systemic manifestations, and (2) to identify potential differences between the systemic manifestations of SpA and those observed in the systemic phase of SD.

Ancillary aims were (1) to identify risk factors for the development of SpA in patients with SD; (2) to highlight age-based differences in the study groups.

2.2. Study design and data collection

An observational study was performed with a retrospective design. Demographic, clinical, biological, radiologic, and therapeutic data were collected from the clinical charts of patients treated at Azienda Ospedaliero-Universitaria Senese and University Children's Hospital Ljubljana, leveraging the data collection instruments of the Auto-inflammatory Diseases Alliance (AIDA) Network Still's disease registry [16], the AIDA Network Undifferentiated Auto-inflammatory Diseases registry [17] and the CATTEDRA registry [available at https://www.better.care/client-story/cattedra/]. Specifically, some of the patients enrolled in the main study group

(SpA with systemic inflammatory manifestations) were previously described in a study by Vitale et al., which included patients from the AIDA Network Undifferentiated Auto-inflammatory Diseases registry up to November 2022 [7].

2.3. Inclusion criteria and operative definitions

Patients were enrolled in three study groups.

The main study group, defined as systemic (S)-SpA group, included subjects of any age with a diagnosis of SpA as per the ILAR criteria [18] or the provisional PRINTO criteria [19] for JIA-ERA (both applicable in the pediatric age) or the ASAS criteria [20] for axial SpA (applicable in adult age), and a history of monocyclic or recurrent fever with unexplained systemic inflammation, defined as the presence of body temperature $\geq 38\,^{\circ}$C accompanied by a clear inflammatory biological signature (including WBC and ESR/CRP > UNL). To be eligible for inclusion in the S-SpA group, patients presenting with fever of unknown origin must have previously undergone a comprehensive diagnostic work-up to rule out infectious, autoimmune, and neoplastic diseases.

The first control group, namely the SD group, included subjects of any age with a diagnosis of SD as per the ILAR criteria or the provisional PRINTO criteria for sJIA (both applicable in the pediatric age) or the Yamaguchi criteria [21] or Fautrel criteria [22] for adult-onset Still's disease (both applicable in the adult age) and absence of SpA features as defined above.

The second control group, defined as SpA group, included subjects of any age with a diagnosis of SpA according to the ILAR, PRINTO or ASAS criteria and absence of the systemic manifestations detailed for the S-SpA group.

Given the purpose of this study, exclusion criteria foreseen by the ILAR classification did not apply [18].

When comparing the three study groups, corrections for age groups were performed. With this regard, the pediatric group was defined as patients with onset of the disease (systemic or articular symptoms of SpA or systemic symptoms of SD) before 18 years [19].

2.4. Ethical considerations

The protocols of the AIDA and CATTEDRA registries were approved by their respective Ethics Committees, namely Tuscany Region Ethics Committee – South-East area (CEAVSE) on 24/06/2019 (Ref. N. 14951) for the AIDA registries and the Slovenian National Ethics Committee for Research in Medicine on 15/12/2020 (Ref. N. 0120-536/2020/3) for the CATTEDRA registry. Patients' data were extracted separately from the two registries and analyzed. Patients were enrolled on a voluntary basis; the written consent/assent provided by the patient (or the parents or legal representatives in case of minors) was considered among mandatory inclusion criteria; values, rights and interests of the research participants were protected as addressed by the World Medical Association Helsinki declaration 2013 [23]. Separation of personally identifiable information and medical data by using double-pseudonymization for storing medical data ensured the compliance to international and local data protection regulations.

2.5. Statistical methods

Data were analyzed using the Jupyter Notebook (available at https://jupyter.org/) via EDINA's Noteable platform, a cloud-based application providing access to coding environments (https://noteable.io/). Descriptive statistics included counts and frequencies for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) and range for continuous variables. Shapiro–Wilk test was used to assess normality distribution of data. Associations between categorical

Table 1
Comparison of the demographic characteristics of patients in the three study groups.

Variables	S-SpA	SD	SpA
Sex (male), *n* (%)	20 (48.8%)	13 (33.3%)	13 (31%)
Adult-onset, *n* (%)	25 (61%)	20 (51.3%)	26 (61.9%)
Age (years), median (IQR)	38.6 (24.9)	30.7 (20.8)	36.4 (31.1)
Age at onset of the disease (years), mean (SD)	28.6 (19.0)	21.9 (18.7)	27.6 (17.5)
Age at onset of systemic symptoms (years), mean (SD)	29.0 (18.7)	21.9 (18.7)	–
Age at onset of SpA symptoms (years), mean (SD)[a]	36.9 (18.9)	–	27.6 (17.5)
Positive familial history[b]	21.5%	11.4%	40.5%
Systemic disease duration (years), median (IQR)	7.2 (6.5)	9.5 (9)	–
SpA duration (years), median (IQR)[c]	1.1 (2.3)	–	3.3 (6.5)

IQR: interquartile range; SD: standard deviation; Sd: Still's disease; SpA: spondyloarthritis; S-SpA: systemic spondyloarthritis.

[a] *P* < 0.05 [N.S. after correcting for age groups].

[b] *P* = 0.01.

[c] *P* < 0.01 [after correcting for age groups, statistical significance was maintained only in the adult-onset group (*P* < 0.05)].

variables were analyzed using Fisher's exact or Chi^2 test with Yates continuity correction. Differences in continuous data between independent groups were compared by Mann–Whitney U test (2 groups) or Kruskal–Wallis H test with Dunn's post-hoc test (more than 2 groups). Univariate analysis was employed to identify possible predictors to be included in the logistic regression analysis. The Bonferroni method was used to correct the level of statistical significance when multiple comparisons were performed. Otherwise, the threshold for statistical significance was set to *P* < 0.05 and all *P*-values were two-sided.

3. Results

We enrolled 122 subjects: 41 in the S-SpA group, 39 in the SD group and 42 in the SpA group. The demographic characteristics of the three groups are detailed and compared in Table 1. The results of the preliminary analysis of age-related differences within the study groups are available as Supplementary Material (Tables S1–S3). Median age at disease onset was 30.1 (IQR: 34.0) years in S-SpA, 18.0 (IQR: 23.3) years in SpA, and 17.2 (IQR: 28.8) years in SD (N.S.). Median age at the onset of SpA manifestations was higher in the S-SpA group (36.7, IQR: 34.0 years) compared to the SpA group (18.0, IQR: 23.3 years) (*P* < 0.05).

3.1. Description of the S-SpA cohort

When analyzing the 41 patients in the S-SpA group, systemic symptoms came first in 30 cases (73.2%), SpA came first in 3 (7.3%), while the clinical pictures were concomitant in 8 (19.5%). The median latency between the first and the second clinical picture (systemic symptoms and SpA) was 4.4 (IQR: 7.2) years (0.0–46.2). No triggers of the shift were identified in 39 cases (95.1%), while isotretinoin for acne and chemotherapy for lymphoma were recently started in 1 patient (2.4%) each.

For patients with S-SpA, the nosological classification was USAID in 30 cases (73.2%), SD in 7 (17%), synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome in 1 (2.4%), chronic recurrent multifocal osteomyelitis (CRMO) in 1 (2.4%), enthesitis-related arthritis in 1 (2.4%), and "clinical" familial Mediterranean fever in 1 (2.4%). Nine subjects (22%) (5 in the pediatric-onset group and 4 in the adult-onset group) carried mutations in genes associated with auto-inflammatory diseases (Table S4).

The first clinical condition (systemic picture or SpA) was active at the onset of the second one in 34 patients (82.9%), it was inactive in 7 (17.1%). In 26 cases (63.4%), the patient was being treated for the first disease when the second one occurred: in 7 cases with non-steroidal anti-inflammatory drugs (NSAIDs) (17.1%), in 10 with corticosteroids (CS) (24.4%), in 6 with colchicine (14.6%), in 6 with

conventional disease-modifying anti-rheumatic drugs (cDMARDs) (14.6%), in 7 with biologic (b)DMARDs (17.1%).

The following systemic complications were observed during the disease course in 7 patients (17.1%): acute hepatitis in 1 patient (2.4%), appendectomy in 1 (2.4%), acute pancreatitis in 1 (2.4%), macrophage activation syndrome in 2 (4.9%), pulmonary emphysema in 1 (2.4%), short stature in 2 (4.9%), hip replacement in 2 (4.9%), osteoporosis in 2 (4.9%), knee surgery in 1 (2.4%), cervical spine surgery in 1 (2.4%), cataract in 1 (2.4%).

3.2. Analysis of systemic manifestations

As for the systemic manifestations of the disease, all patients in the S-SpA group had fever as per the inclusion criteria. The higher body temperature reached during the attack was median (IQR) 39 (1.1) °C. The frequency of clinical manifestations accompanying fever in the systemic phase is reported in Fig. 1A. Skin rash was erythematous in 5 patients (12.2%), salmon-colored evanescent in 5 (12.2%), urticarial in 5 (12.2%), maculo-papular in 3 (7.3%), pustular in 3 (7.3%), being these morphologies variably associated in the same patient. Serosal inflammation involved the pericardium in 3 cases (7.3%), the pleura in 5 (12.2%) and the peritoneum in 1 (2.4%). Enlarged lymph nodes were observed at the cervical (*n* = 16, 39%), axillary (*n* = 8, 19.5%), inguinal (*n* = 6, 14.6%), retro-auricular (*n* = 1, 2.4%), and visceral sites (*n* = 10, 24.4%). Less common symptoms included arrhythmia in 3 patients (7.3%), xerophthalmia in 3 patients (7.3%), night sweating and superficial venous thrombosis in 1 patient each (2.4%).

Differences in the frequency of systemic manifestations between the S-SpA and the SD groups are represented in Fig. 2. By age group stratification, skin rash (*P* = 0.04) and hepato-splenomegaly (*P* < 0.01) maintained its association with SD only in the adult-onset subgroup, while gastrointestinal symptoms (*P* = 0.01), headache (*P* < 0.01), recurrent oral ulcers (*P* < 0.01) and conjunctivitis or periorbital edema (*P* < 0.05) were associated to S-SpA only in the pediatric-onset subgroup. After applying the Bonferroni correction for multiple comparisons, statistical significance was retained only by headache (*P* < 0.01) and recurrent oral ulcers (*P* < 0.01) in the pediatric-onset group.

The results of laboratory tests performed during the systemic phase in the S-SpA and SD groups are compared in Table S5.

3.3. Analysis of SpA manifestations

For patients with SpA, the nosological classification was radiographic or non-radiographic SpA in 21 cases (50.0%), JIA-ERA in 10 (23.8%), psoriatic arthritis in 6 (14.3%), SAPHO syndrome in 2 (4.8%), enteropathic arthritis in 1 (2.4%), Behçet's disease in 1 (2.4%), and Sonozaki syndrome in 1 (2.4%).

A

B
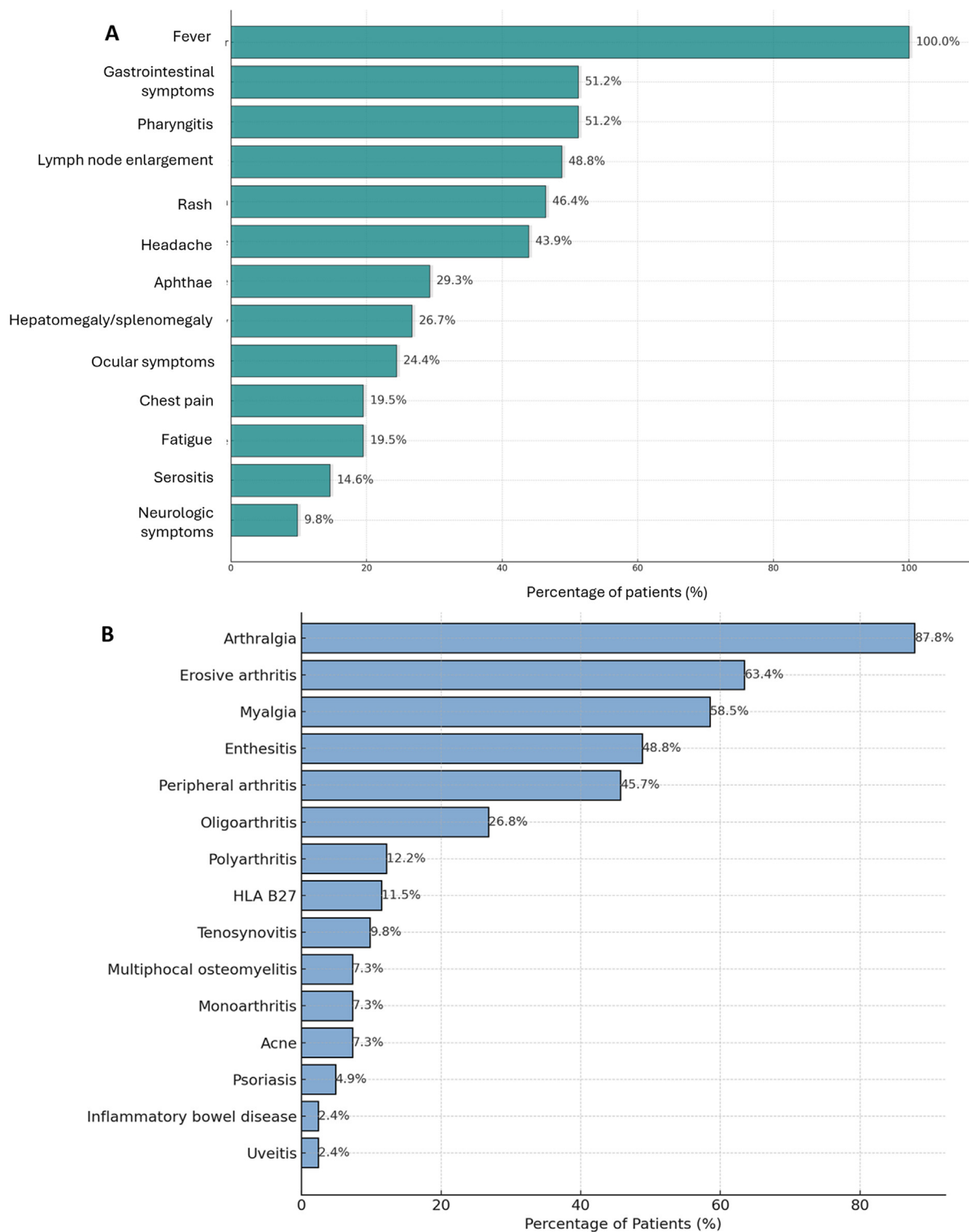
Fig. 1. Frequency of clinical manifestations recorded during the systemic phase (A) and at the onset of spondyloarthritis (SpA) (B) in the systemic (s)-SpA cohort.

The frequency of SpA manifestations in the S–SpA group is reported in Fig. 1B. In the S–SpA group, HLA-B27 was present in 3 patients (7.3%), absent in 23 (56.1%), unknown in 15 (36.3%), while in the SpA group it was present in 10 patients (23.8%), absent in 17 (40.5%), unknown in 15 (35.7%) (N.S.).

When compared to the SpA group, patients with S–SpA had less frequently uveitis (2.4% versus 28.6%, $P < 0.01$) and a familial history of HLA-B27-associated diseases (7.3% versus 33.3%, $P < 0.01$);

on the contrary, tenosynovitis was reported more frequently in the S–SpA group (9.8% versus 7.1%, $P = 0.01$). The prevalences of enthesitis, axial arthritis, peripheral arthritis and erosive arthritis were similar between the two groups (N.S. for all of them). There were no significant differences in the frequency of involvement of each peripheral joint between the S–SpA and the SpA groups (N.S. for all of them). Details of the patterns of joint involvement in the S–SpA and SpA groups are provided as Table S6.
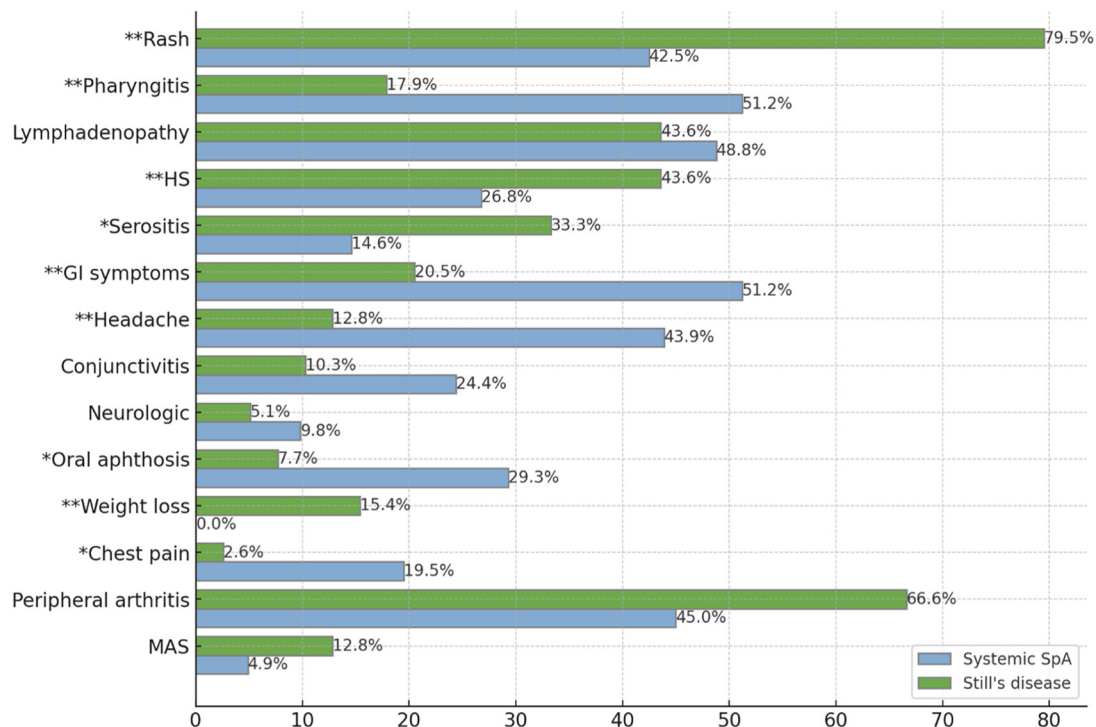
Fig. 2. Comparison between the systemic spondyloarthritis (S-SpA) and Still's disease (SD) patients according to the frequency of systemic manifestations accompanying fever. *$P < 0.05$; **$P < 0.01$. GI: gastrointestinal; HS: hepato-splenomegaly; MAS: macrophage activation syndrome.

By age group stratification, uveitis was associated to SpA in both the pediatric-onset and the adult-onset group ($P < 0.01$) while familial history was associated with SpA only in the pediatric-onset one ($P < 0.01$); on the other hand, S-SpA was associated with tenosynovitis ($P < 0.05$) and erosive arthritis ($P < 0.05$) only in the pediatric-onset group. When applying the Bonferroni correction for multiple comparisons, only the presence of uveitis was significantly associated with SpA in both age groups.

The results of laboratory tests performed at the onset of SpA in the S-SpA and SpA groups are compared in Table S5.

3.4. Analysis of radiological characteristics of SpA

Signs of inflammation and damage detected by sacroiliac magnetic resonance imaging (MRI) in patients with S-SpA and SpA are detailed in Fig. 3A. The prevalence of sacroiliac inflammatory and structural damage signs was similar between the S-SpA and SpA groups, also stratifying the population according to age at disease onset (N.S. for all signs). The frequency of spine inflammatory signs detected by MRI was different in patients with S-SpA and SpA, as detailed in Fig. 3B. After applying the Bonferroni correction for multiple comparisons, inflammation at the facet joints ($P < 0.01$) and inter-apophyseal capsulitis ($P < 0.01$) retained the statistical significance, resulting more frequent in the SpA and S-SpA groups respectively. After stratification based on age at disease onset, only inter-apophyseal capsulitis in adult-onset disease showed a significant difference between the S-SpA and SpA groups ($P = 0.01$).

Iconographic material from sacroiliac and spine MRI of subjects from the S-SpA and SpA groups is available as Table S7.

3.5. Analysis of treatment strategies

The frequencies of different treatment choices in the three study groups are detailed and compared in Table 2.

As for therapeutic efficacy, systemic corticosteroids (CS) prescribed for active systemic symptoms showed complete efficacy in 5 (17.9%) S-SpA and 26 (66.7%) SD patients, partial efficacy in 15 (53.6%) S-SpA and 12 (30.8%) SD patients, and failure in 8 (28.6%) S-SpA and 1 (2.6%) SD patients ($P < 0.01$). Methotrexate (MTX) prescribed for active systemic symptoms showed complete efficacy in 1 (10.0%) S-SpA and 14 (50.0%) SD patients, partial efficacy in 8 (80.0%) S-SpA and 14 (50.0%) SD patients, and failure in 1 (10.0%) S-SpA and 0 (0.0%) SD patients ($P < 0.05$). No statistically significant differences were found in the therapeutic efficacy of colchicine (N.S.), cyclosporin A (N.S.), anakinra (N.S.), canakinumab (N.S.) and adalimumab (N.S.).

As for the drugs prescribed for active SpA symptoms, no statistically significant differences were found in the therapeutic efficacy of systemic CS ($P = 0.05$), MTX (N.S.), sulfasalazine (N.S.) and adalimumab (N.S.). The efficacy of other molecules employed could not be compared between groups because of the very low counts.

3.6. Analysis of subjects with SD who developed SpA

Forty-eight subjects were classified as SD according to the PRINTO ($n = 21$), ILAR ($n = 13$) or Yamaguchi ($n = 28$) criteria. Among them, 9 (18.8%) developed SpA. The clinical characteristics of these 9 patients are detailed in Table 3. Patients with SD who developed SpA showed more frequent pharyngitis [6/9 (66.7%) versus 7/39 (17.9%) with $P = 0.01$]; also, a lower frequency of complete response to systemic CS during the systemic phase of the disease was observed in this subset [1/8 (12.5%) versus 26/39 (66.7%) with $P < 0.05$]. These variables were imputed in the logistic regression analysis, revealing that the complete efficacy of systemic CS during the systemic phase of the disease significantly reduced the likelihood of developing SpA in individuals classified as SD (OR = 0.06, coefficient −2.87 [CI: −5.0 to −0.8]) while the presence of pharyngitis significantly increased the likelihood of developing SpA (OR: 18.19, coefficient: 2.90 [CI: 0.43–5.38]) with $P < 0.01$.
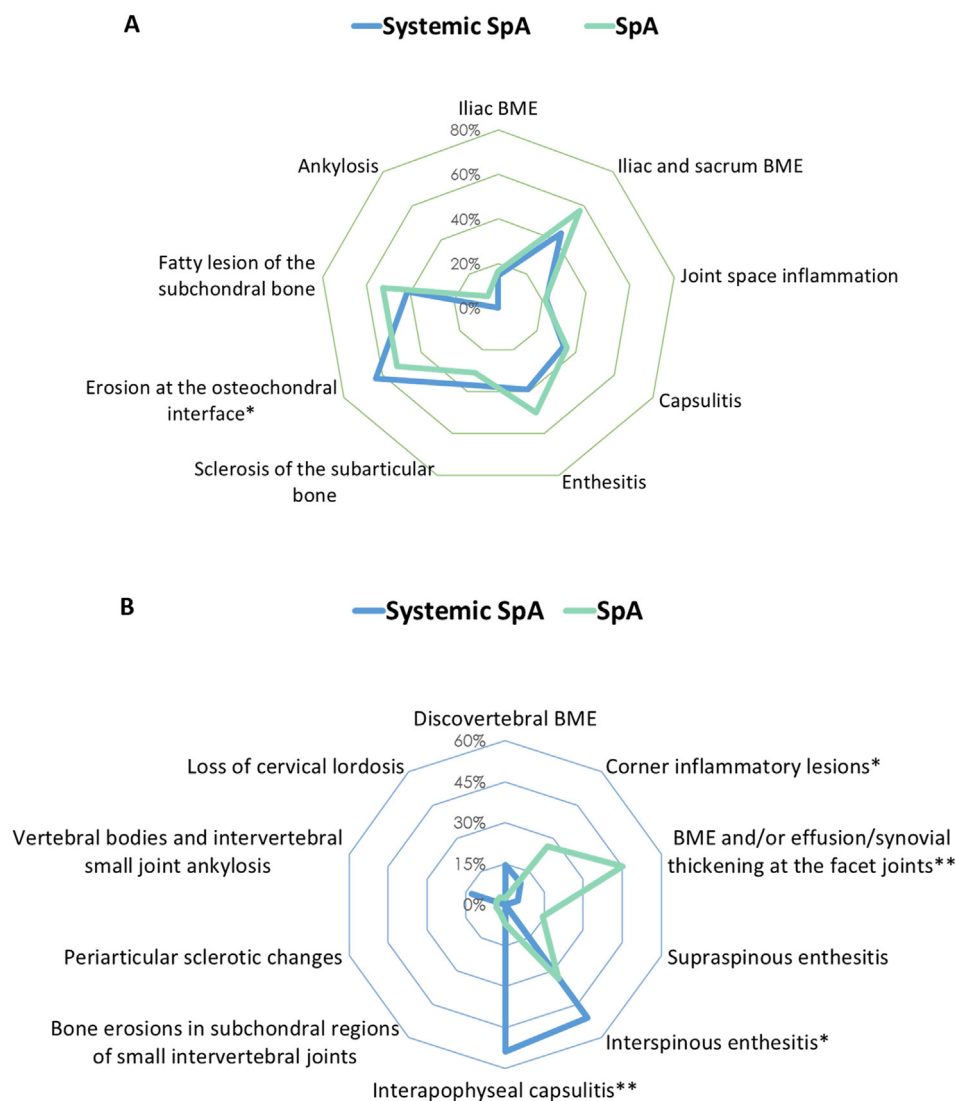
Fig. 3. Comparison between systemic spondyloarthritis (S-SpA) and SpA patients according to inflammatory and structural damage signs detected by magnetic resonance imaging of the sacroiliac joints (A) and the spine (B). *P < 0.05; **P < 0.01. BME: bone marrow edema.

4. Discussion

Fever and systemic inflammatory symptoms may be part of the clinical picture of SpA at the onset or during the course of the disease. Nevertheless, the pathophysiological basis of this clinical association is poorly understood and, consequently, its nosological classification remains inadequately defined. In our cohort, we observed instances of S-SpA presenting within distinct clinical entities, including SAPHO syndrome, chronic recurrent multifocal osteomyelitis, SD, or FMF; however, in the majority of cases, this condition came across as either an isolated finding or accompanied by systemic inflammatory manifestations resembling USAID. In this cohort, the age at disease onset was similar for both S-SpA and SpA in pediatric-onset and adult-onset cases. However, in the S-SpA group, articular symptoms tended to follow the systemic-onset, accounting for the observed difference in the age at onset when only considering articular manifestations.

Subjects with S-SpA not fulfilling any diagnostic criteria for other systemic inflammatory diseases capable to explain the clinical picture have been reported both in the pediatric and in the adult age. The systemic presentation at onset will usually be described as a sepsis-like picture, with high spiking fever, weight loss, night sweats, a toxic appearance, remarkable increase of acute phase

response markers, inflammatory micro- or normocytic anemia, leukocytosis and thrombocytosis [9–11,24,25]. Notably, low-to-moderate grade of fever affected the vast majority of children described by Guo et al., and "irregular", "intermittent" and "remittent" patterns were reported in their pediatric cohort [8].

Vitale et al. recently identified a subgroup of adults with SpA experiencing recurrent fever attacks, termed 'febrile SpA', with a quarter reporting onset in childhood, partially overlapping with our cohort from the AIDA Network USAID registry [7]. Unlike most literature that associates fever and peripheral arthritis with axial SpA, this phenotype shows a wider range of inflammatory symptoms, extending to gastrointestinal and muco-cutaneous manifestations, lymph node enlargement, pharyngitis and chest pain, more closely mirroring auto-inflammatory diseases. In this context, the findings of our study reveal that the S-SpA phenotype distinctly diverges from the classical SD phenotype observed during the systemic phase, in terms of both clinical presentations and laboratory markers. Furthermore, approximately 20% of the patients were found to harbor mutations in genes associated with monogenic auto-inflammatory diseases, although these mutations did not fully explain the clinical picture, as they did not meet the confirmatory genotype and pertinent clinical manifestations. Nevertheless, low-penetrance mutations in genes typically associated with auto-

Table 2

Use of different drugs in patients with S-SpA, SD or SpA to treat the systemic symptoms and/or the articular manifestations of the disease.

	Drugs started for active systemic symptoms	
	S-SpA	SD
Systemic CS**	29 (74.4%)	39 (100.0%)
cDMARDs**	27 (69.2%)	38 (97.4%)
Colchicine**	19 (48.7%)	6 (15.4%)
MTX**	10 (25.6%)	32 (82.1%)
CsA*	2 (5.1%)	10 (25.6%)
HCQ	5 (12.8%)	2 (5.1%)
SSZ/MSZ	4 (10.3%)	1 (2.6%)
CYC	1 (2.6%)	0 (0.0%)
TCR	0 (0.0%)	2 (5.1%)
bDMARDs**	19 (46.3%)	34 (87.2%)
ANA	8 (19.5%)	15 (38.5%)
CAN	5 (12.2%)	13 (33.3%)
TCZ**	1 (2.4%)	19 (48.7%)
ETN	2 (4.9%)	4 (10.3%)
ADA	5 (12.2%)	12 (12.8%)
IFX	3 (7.3%)	6 (15.4%)
SEC	1 (2.4%)	0 (0.0%)

	Drugs started for active SpA symptoms	
	S-SpA	SpA
Systemic CS	12 (33.3%)	11 (28.2%)
cDMARDs	16 (39.0%)	21 (50.0%)
Colchicine	6 (14.6%)	2 (4.8%)
MTX	8 (19.5%)	10 (23.8%)
CsA	0 (0.0%)	1 (2.4%)
HCQ	2 (5.0%)	0 (0.0%)
SSZ*	5 (12.5%)	15 (35.7%)
bDMARDs*	24 (58.5%)	36 (85.7%)
ETN	0 (0.0%)	9 (21.4%)
ADA	21 (51.2%)	26 (61.9%)
IFX	2 (4.9%)	7 (16.7%)
CZP	0 (0.0%)	1 (2.4%)
GOL	0 (0.0%)	8 (19.1%)
SEC	1 (2.4%)	1 (2.4%)
TCZ	1 (2.4%)	0 (0.0%)
ANA	2 (4.9%)	0 (0.0%)
CAN	3 (7.3%)	0 (0.0%)
JAKi	2 (4.9%)	1 (2.4%)
TOFA	2 (4.9%)	0 (0.0%)
UPA	0 (0.0%)	1 (2.4%)

ADA: adalimumab; ANA: anakinra; bDMARDs: biologic disease-modifying anti-rheumatic drugs; CAN: canakinumab; cDMARDs: conventional disease-modifying anti-rheumatic drugs; CS: corticosteroids; CsA: cyclosporin A; CYC: cyclophosphamide; CZP: certolizumab Pegol; ETN: etanercept; GOL: golimumab; HCQ: hydroxychloroquine; IFX: infliximab; JAKi: Janus kinases inhibitors; MSZ: mesalazine; MTX: methotrexate; SD: Still's disease; SEC: secukinumab; SpA: spondyloarthritis; S-SpA: systemic spondyloarthritis; SSZ: sulfasalazine; TCR: tacrolimus; TCZ: tocilizumab; TOFA: tofacitinib; UPA: upadacitinib.

* $P < 0.05$.

** $P < 0.01$.

inflammatory diseases can still influence the patient's phenotype in milder or more varied ways, often interacting with additional genetic or epigenetic factors. Therefore, while the role of the detected variants in modifying the SpA phenotype cannot be excluded, further research using a different approach would be needed to substantiate this hypothesis.

In our S-SpA cohort, we observed a low frequency of the HLA-B27 allele (7.3%), although the amount of missing data was considerable. However, the notably lower frequencies of uveitis and HLA-B27-related disease familial history may suggest a weaker association of this genetic locus with S-SpA than axial SpA. Similarly, Byun et al. compared 26 S-SpA patients with 100 axial SpA patients, observing a lower frequency of HLA-B27 in the former group (52.2% vs. 77.0%) [9]. In addition, it is important to highlight that familial aggregation was lower in the S-SpA group compared to the SpA group in this study. This finding can be at least

partially explained by the nosological entities included under the S-SpA umbrella, which are mainly considered to have a multifactorial etiology, such as USAID, SD, and SAPHO syndrome/CRMO. Axial SpA is currently recognized as a heterogeneous group of clinical entities, each underpinned by unique pathogenetic mechanisms and genetic background, and in this context HLA-B27 accounts for only a portion of the genetic predisposition [1,26]. A parallelism may arise with the association of FMF with SpA, whose genetic factors appear more likely dependent on *MEFV* gene mutations – especially with the M694V variant – rather than HLA-B27 [27–29]. The analogy with the FMF-SpA phenotype extends to the radiological features of S-SpA as well, which appears to show less radiographic evidence of spinal involvement, including the presence of syndesmophytes, compared to axial SpA [29–32]. In this context, a comprehensive analysis of the clinical, genetic, and radiological characteristics of SpA within both monogenic and multifactorial auto-inflammatory diseases would significantly advance our understanding of this complex condition. This analysis should especially focus on FMF, with recent studies using advanced diagnostic techniques estimating a SpA prevalence of up to 26%, and Behçet's disease, due to genetic associations indicating shared MHC-I-associated immuno-pathogenic mechanisms in both Behçet's disease and SpA [1,33].

The clinical profile delineated herein exhibits a potential for remarkable severity, as evidenced by the identification of systemic and skeletal complications, along with long-term consequences related to drug usage and uncontrolled inflammation. In this regard, Guo et al. identified fever as an adverse prognostic indicator in children with ERA, affecting the severity of arthritis and enthesitis, the MRI findings, the levels of inflammatory markers, and the necessity for treatments [8]. It's important to note that only a minority of our S-SpA cohort (17%) experienced complications, with similar rates of enthesitis, peripheral arthritis and erosive arthritis observed in both S-SpA and SpA groups. Comparable percentages of patients in both groups showed BME at the ileum or sacrum and they had similar biological markers of inflammation at SpA onset. This latter finding is consistent with the long delay between systemic and SpA manifestations, differently from what was observed in the study by Guo et al. [8].

The concomitant occurrence of SpA and SD deserves a special mention. Since the late twentieth century, it is known that around 11% of subjects with juvenile-onset ankylosing spondylitis and 6% of those with juvenile-onset undifferentiated SpA may be characterized under the SD classification due to the presence of SD typical clinical and laboratory picture at onset and/or during subsequent active phases [34,35]. More recently, they estimated the prevalence of SpA in the French adult and pediatric population affected by SD as 6.58% (95% CI: 2.17–14.69) and 10% (95% CI: 2.11–26.53), respectively, significantly exceeding the prevalence found in the general population [12]. The two phenotypes were concomitant in most patients described in the literature and also in three patients out of nine from our series [12,14,15,34,35]. For these patients, particularly in cases with a monocyclic course of the systemic manifestations, we consider that a febrile onset of SpA, temporarily meeting the classification criteria for SD, cannot be ruled out.

On the other hand, SD preceded SpA onset by years in the remaining six patients from this study and in six subjects from the abovementioned French cohort, all being HLA-B27 negative [12]. Interestingly, also the opposite situation has been reported – SpA preceding SD – in a minority of cases [12,36]. For at least a subset of our patients, where SD was still active during the onset of SpA, SpA could represent the progression of a widespread, inadequately managed disease (treated with remarkable delay or in the pre-biologic era) resulting in a severe clinical picture. With this regard, the failure to fully respond to CS during the systemic phase was an indicator of the progression to SpA in patients

Table 3
Characteristics of 9 patients diagnosed with Still's disease and spondyloarthritis.

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Sex	F	F	F	M	M	M	F	M	M
Age at onset of SD	30.3	52.8	50.2	42.0	31.5	30.3	46.0	4.2	3.0
Age at axial involvement	37.3	57.6	52.4	46.5	31.5	30.3	46.0	6.6	< 18
SD activity when axial arthritis occurred	No	–	–	–	–	–	–	–	–
Triggers	–	–	–	–	–	–	–	–	–
Ongoing therapy when axial arthritis occurred	–	NSAIDs, MTX and CAN with complete efficacy	HCQ with partial efficacy	CS with partial efficacy	–	–	–	CS, MTX with partial efficacy	CS, MTX with partial efficacy
SD treatment delay (m)	1	–	14	12	11	–	–	12	1
Systemic involvement	BT 42 °C, salmon evanescent and urticarial rash, pharyngitis, generalized lymph node enlargement, hepato-splenomegaly, uveitis	BT 40 °C, salmon evanescent rash, pharyngitis, pleural effusion, aseptic meningo-encephalitis	BT 40 °C, pharyngitis, splenome-galy	BT 39.5 °C, pharyngitis, generalized lymph node enlargement, abdominal pain, fatigue, conjunctivi-tis, night sweating	BT 39 °C, salmon evanescent rash, MAS	BT 39 °C, salmon evanescent rash, abdominal pain, acute hepatitis	BT 39 °C, salmon evanescent rash, pharyngitis, lymph node enlargement, abdominal pain	BT 40 °C, skin rash, pharyngitis, pleural and pericardial effusion, abdominal pain, MAS, growth failure	BT > 38 °C, hepato-splenomegaly, growth failure
Articular involvement	Polyarthritis, axial arthritis, enthesitis	Myalgia, oligoarthritis, axial arthritis	Myalgia, arthralgia, axial arthritis, enthesitis	Oligoarthritis, axial arthritis, myalgia, enthesitis	Myalgia, polyarthritis, axial arthritis	Myalgia, oligoarthritis, axial arthritis	Oligoarthritis, axial arthritis	Myalgia, polyarthritis, axial arthritis, tenosynovi-tis, hip replacement	Oligoarthritis, axial arthritis, hip replacement, cervical spine surgery
Therapy after axial involvement	CS and NSAIDs (partial response)	NSAIDs, CAN, increased MTX (response NA)	MTX and ADA (partial), MTX and TOFA (complete)	NSAIDs, MTX (failure), ADA (partial), IFX (partial)	MTX and CAN (complete)	NA	MTX and ANA (partial)	IFX (partial)	NA

ADA: adalimumab; ANA: anakinra; BT: body temperature; CAN: canakinumab; CS: corticosteroids; F: female; HCQ: hydroxychloroquine; IFX: infliximab; M: male; m: months; MAS: macrophage activation syndrome; MTX: methotrexate; NA: not available; NSAIDs: non-steroidal anti-inflammatory drugs; SD: Still's disease; TOFA: tofacitinib.

with SD in our study group. This observation suggests that prolonged inflammation might play a key role in shifting towards a 'type 3 immunity' profile. Indeed, it has been demonstrated that high concentrations of IL-1, IL-6, and S100A12 can prime γδT cells for increased IL-17 expression and this latter cytokine was found to be elevated in patients with active SD [37]. Interestingly, two of our patients developed SpA when SD was in remission on or off medications. In this respect, prior research on SD patients has shown that neutrophils exhibit an enhanced capacity for S100A8/A9 alarmin release upon activation, even in remission, and maintain a high pro-inflammatory gene expression profile despite prolonged successful biologic treatment [38]. The involvement of neutrophils is particularly intriguing in this context, as recent evidence indicates these cells transcend their traditional role as terminal effectors, also promoting T helper 17 and type 17 CD8+ T cells development through the secretion of IL-23 and proteases, and the formation of neutrophil extracellular traps (NETs) [39].

By exploring the auto-inflammatory side of SpA, this study intercepts a recent paradigm shift that would redefine axial SpA as a primary inflammatory condition of the bone marrow where dysfunctional immune cells may create a pro-inflammatory milieu in response to mechanical stress transduced by the enthesis [40]. In this context, a major drawback of our study is the lack of a cytokine profiling of our patients and the limited availability of genetic

data – including the HLA-B27 allele which was not tested or not reported for many subjects – due to the retrospective nature of data collection. This limitation precludes the establishment of any pathophysiological connection between the onset of axial inflammation and the 'cytokine burst' behind the systemic manifestations observed in our patients. Moreover, the heterogeneity within the S-SpA and SpA groups introduces significant challenges in interpreting our results, particularly the radiologic ones, which may be skewed by the inclusion of diseases that predominantly affect either the bone or the soft tissues [26]. Conversely, the decision to encompass both pediatric and adult patients within the cohort emerged as a substantial strength of this study enabling the detection of many instances where a significant delay occurred between the presentation of systemic and SpA symptoms. In this regard, it is important to emphasize that for 83% of our patients, the initial clinical condition (either systemic involvement or SpA) was active at the onset of the second condition. This indicates that for the majority of patients, febrile episodes were recurrent up to the SpA diagnosis, or a single febrile episode coincided with the onset of SpA, thereby temporarily linking the two phenotypes. For the minority of patients in whom the systemic disease (specifically Still's disease or USAID) was inactive at the time of SpA onset, both the coincidence of two distinct diagnoses and the potential role of subclinical inflammation in triggering SpA onset cannot be excluded.

5.

In conclusion, spondyloarthritis should be ruled out in adult and pediatric patients presenting with unexplained systemic inflammatory manifestations. This diagnostic consideration should extend beyond the domains of well-defined auto-inflammatory disorders such as FMF, Behçet's disease, or SAPHO syndrome, to also include USAID and SD. When there exists a clinical suspicion of S-SpA, sacroiliac MRI scans may offer superior diagnostic utility over spine scans in identifying the hallmark signs of axial inflammation. The association of S-SpA with the HLA-B27 allele appears to be less pronounced, mirroring observations in MHC-I-related diseases. Nonetheless, further investigative efforts are necessary to elucidate the pathophysiological mechanisms connecting the systemic and axial manifestations of the disease.

Ethics statements

The protocols of the AIDA and CATTEDRA registries were approved by their respective Ethics Committees, namely Tuscany Region Ethics Committee – South-East area (CEAVSE) on 24/06/2019 (Ref. N. 14951) for the AIDA registries and the Slovenian National Ethics Committee for Research in Medicine on 15/12/2020 (Ref. N. 0120-536/2020/3) for the CATTEDRA registry. Patients participating in the study, or their parents or legal representatives in the case of minors, provided written consent or assent for participation in the study. Values, rights and interests of the research participants were protected as addressed by the World Medical Association Helsinki declaration 2013.

Consent for publication

Not applicable.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure of interest

The authors declare that they have no competing interest.

Author contributions

Carla Gaggiano: conceptualization, data curation, formal analysis, writing – original draft, visualization, funding acquisition; Mojca Zajc Avramovič: resources, data curation, writing – review & editing; Antonio Vitale, Nina Emeršič, Stefano Gentileschi, Maria Tarsia, Gašper Markelj, Tina Vesel Tajnšek, Claudia Fabiani, Anja Koren Jeverica: resources; Jurgen Sota and Valeria Caggiano: resources, data curation; Nataša Toplak: resources, supervision, writing – review & editing; Bruno Frediani: funding acquisition, supervision; Maria Antonietta Mazzei: resources, data curation, supervision; Luca Cantarini: conceptualization, funding acquisition, supervision; Tadej Avčin: conceptualization, funding acquisition, writing – review & editing, supervision.

Medical writing/editorial assistance

The authors acknowledge the use of ChatGPT [https://chat.openai.com/] at the final stage of preparing this manuscript for spell/grammar check. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2024.105772.

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