Adult-Onset Still's Disease or Systemic-Onset Juvenile Idiopathic Arthritis and Spondyloarthritis: Overlapping Syndrome or Phenotype Shift?

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Highlights:

- Still's disease and spondyloarthritis can coexist in the same patient.
- The prevalence of spondyloarthritis is higher in patients with Still's disease than the general population.
- This association suggests common pathogenic pathways for the two diseases.

Abstract (250 words)

Objectives. Systemic-onset juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD) are the same sporadic systemic auto-inflammatory disease. Spondyloarthritis (SpA) is a group of inflammatory non-autoimmune disorders. We report the observations of eight patients with SJIA/AOSD who also presented features of SpA during their disease evolution and estimate the prevalence of SpA in SJIA/AOSD.

Methods. This was a retrospective national survey of the departments of paediatric and adult rheumatology and internal medicine. To be included, SJIA patients had to fulfil the ILAR criteria, AOSD patients the Yamaguchi or Fautrel criteria, and all patients the ASAS classification criteria for axial or peripheral SpA, ESSG criteria for spondyloarthropathy or CASPAR criteria for PsA. The data were collected with a standardized form.

Results. Eight patients (five adults) were identified in one paediatric and two adult departments. In all but one patient, SpA manifestations occurred several years after SJIA/AOSD onset (mean delay 6.2±3.8 years). Two patients had peripheral and three axial SpA, and four later exhibited PsA and one SAPHO syndrome. The prevalence of SpA in an adult cohort of 76 patients with AOSD was 6.58% (95% CI [2.17-14.69]), greater than the prevalence of SpA in the French general population (0.3%, 95%CI [0.17-0.46]). The prevalence of SpA in an SJIA cohort of 30 patients was 10% (95%CI [2.11-26.53]), more than that reported in the general population of industrialized countries, estimated at 0.016% to 0.15%.

Conclusion. The association of both diseases in the same patient suggests common pathogenic pathways between SJIA/AOSD and SpA.

Introduction

Childhood-onset Still's disease, today called systemic-onset juvenile idiopathic arthritis (SJIA), and adult-onset Still's disease (AOSD) represent the same sporadic systemic auto-inflammatory disorder with inappropriate activation of the innate immune system (1,2). This condition involves innate immunity and dysregulated activation of macrophages and neutrophils in response to a danger signal leading to tissue damage (1). Still's disease is traditionally characterized by four cardinal manifestations: spiking fever, an evanescent salmon-pink maculopapular rash, arthralgia or arthritis and white-blood-cell count (WBC) ≥10,000/mm3, mainly neutrophilic PMNs. Many other manifestations and complications can be associated, so the clinical presentation is heterogeneous (1). The disease course can also vary and is currently unpredictable. Arthralgia and myalgia are the most common rheumatic manifestations, usually starting concomitantly with fever and with a maximal intensity during fever spikes. Arthritis is present in more than two thirds of patients. "Rheumatoid arthritis-like" polyarthritis (i.e. bilateral, symmetrical and affecting preferentially the distal joints of wrists, hands and feet) has been described (3). Any joint can be involved, more frequently radio-carpal or carpal joints, with the "classical bilateral ankylosing carpal arthritis", which is very suggestive when "isolated" (i.e., without concomitant MCP or PIP structure damage) (1,3,4). The diagnosis is not based on pathognomonic elements but rather on bundles of arguments included in the classification criteria: Yamaguchi and Fautrel criteria for AOSD (5,6) and ILAR criteria for SJIA (7). The Yamaguchi criteria may be useful for classifying childhood SJIA, particularly in the "pre-arthritic", pure systemic, disease phase (8).

At the frontier of autoinflammatory disorders (2,9), spondyloarthritis (SpA), formerly called spondyloarthropathy, describes a heterogeneous group of interrelated rheumatic conditions comprising AS, PsA, arthritis/spondylitis with IBD, reactive arthritis and SAPHO syndrome (10–

13). The SpA pathogenesis is complex (14). For many years, the traditional pathophysiological framework for SpA has been the arthritogenic-peptide theory, which proposes that HLA-B27 presents self-peptides that resemble pathogen-derived peptides to CD8-restricted T lymphocytes (14,15). However, this hypothesis has been seriously challenged by two independent reports showing that CD8 T cells were not needed for disease in HLA-B27 transgenic rats (16,17). New hypotheses argue for an autoinflammatory rather than autoimmune origin because HLA-B27 has a role in triggering innate immune responses rather than its canonical role of antigen presentation (14,17). These new insights have led some authors to propose SpA — or some of its manifestations, such as psoriasis, chronic recurrent multifocal osteomyelitis or SAPHO syndrome — as autoinflammatory disorders (2,9,18). Indeed, the major histocompatibility complex (MHC) class-I–associated diseases, including psoriasis (HLA-Cw6) and AS (HLA-B27), show striking clinical overlaps with Crohn's disease, Behçet's disease and also some rare monogenic diseases. In addition, these diseases are distinct from classical autoimmunity in that specific autoantibodies are absent. This observation points to an interaction between tissue-specific factors and adaptive immunity in the overlapping clinical phenotypes of these disorders (18). Furthermore, genes such as IL-23R also confer a risk for SpA-associated disorders such as Crohn's disease and psoriasis (14).

Here we report the observations of eight patients with SJIA/AOSD who also presented clinical features of SpA during the disease evolution and discuss the possible pathophysiologic link between SJIA/AOSD and SpA.

Patients and methods

Objective

The primary objective was to gather cases of patients with SJIA or AOSD who also presented

features suggesting SpA and to describe their clinical, biological and imaging evolution as well as their therapeutic responses. The secondary objective was to estimate the prevalence of SpA among the active files of each identified centre following SJIA or AOSD patients.

Case identification

This retrospective study was based on a national survey of the departments of paediatric or adult rheumatology and internal medicine in all French hospitals with an online call from the *Club Rhumatismes et Inflammation* (http://www.cri-net.com) to physicians actively involved in managing Still's disease in France. To be included in the cross-sectional study, SJIA patients had to fulfil the ILAR criteria (7), and AOSD patients had to fulfil the Yamaguchi or Fautrel criteria (5,6). In addition, all patients had to fulfil at least one of the sets of classification criteria for SpA: ASAS criteria for axial or peripheral SpA, ESSG criteria for spondyloarthropathy, CASPAR criteria for PsA, or Kahn's criteria for SAPHO syndrome (10,11,13,19–21).

Data collection

Three authors (NH, AK, SM) retrospectively collected data by using a standardized form established by one author (SM) and approved by all. The form was used to gather data on SJIA or AOSD as well as SpA manifestations.

Data collected for SJIA and AOSD included sex, date of birth, date of disease onset and duration of follow-up, systemic symptoms at onset (fever, skin rash, pharyngitis, lymphadenopathy, hepatosplenomegaly, and serositis), arthralgia and arthritis, laboratory parameters at onset (haematological profile, first-hour ESR, CRP level, and serum ferritin level; the percentage of glycosylated ferritin was also recorded when available), number of flares, evolution profile, treatments received (corticosteroids, conventional synthetic or biological

DMARDs), and therapeutic response assessed qualitatively as complete remission, partial response or failure. Complete remission under treatment was defined as the absence of any clinical and biological signs of the disease (i.e., the disappearance of fever, arthralgia and arthritis, myalgia, sore throat, rash, adenopathy, hepatosplenomegaly, and the normalization of blood counts, ESR, and CRP and serum ferritin levels). Partial remission corresponded to some improvement noted by the physician in charge of the patient but some systemic, articular, or biologic features persisting after treatment start. Treatment failure was considered if SJIA/AOSD symptoms remained mainly unchanged during treatment.

Data collected for SpA manifestations included the date of onset and SJIA/AOSD disease duration at SpA onset, tender joint count (TJC), swollen joint count (SJC) and number of enthesitis episodes at onset, inflammatory back pain or buttock pain, HLA-B27 status, axial and peripheral radiological features, treatment response (defined above), personal and family medical history of extra-articular manifestations (skin psoriasis, uveitis, IBD or acne) or other rheumatic disease.

Lab values at Still's disease onset are expressed as median [interquartile range (IQR)] because or non-normal distribution; clinical data are expressed as mean ± standard deviation.

Assessment of the active files of the centres that declared a case and prevalence estimation

Each centre that had included at least one patient performed a supplementary screening by using diagnosis-related group and International Classification of Disease codes to identify in its active files of SJIA or AOSD patients cases that also included the diagnosis of SpA. Prevalence was estimated with 95% confidence intervals (CIs for such patients.

Ethics

According to the rules and regulation of clinical research for descriptive retrospective

studies in France, approval of the Ethics Committee was not necessary, and consent was indirectly obtained by non-opposition to the use of the data for research purpose from all patients after information (22).

Results

Three centres (two adult) replied to the online call. Three paediatric cases and 5 adult cases fulfilling both SJIA or AOSD and SpA classification criteria were identified.

General characteristics of patients

Among the eight patients (five males), seven were Caucasian and one African **(**see **Table 1** for characteristics**)**. No consanguinity was reported in any case.

Mean age at data collection was 34.8±18.1 years (SJIA: 18.3±6.6 years; AOSD: 44.8±15.1 years); mean age at SJIA and AOSD onset was 4.3±3.0 and 35.4±13.3 years, respectively. In all but one patient, SpA manifestations occurred after SJIA/AOSD onset (overall mean delay for the two diseases: 6.2±3.8 years; SJIA: 7.4±2.2 years; AOSD 5.2±4.7 years). AOSD was diagnosed 11 years after the diagnosis of SpA in the 9th patient (case 8).

Mean age at SpA onset was 27.5±16.6 years (SJIA: 11.3±1.5 years; AOSD: 37.2±12.8 years) and mean follow-up duration was 10.8±6.0 years (range 3-20).

Data at SJIA and AOSD onset and during disease evolution

All SJIA and AOSD patients had systemic disease expression and presented the four cardinal symptoms at disease onset: mean temperature was 39.1±0.6 °C, arthralgia/arthritis and rash were present in all patients, median WBC count was 18,065 [interquartile range (IQR) 14,399-21,693] /mm^3, (14,290 [IQR 13,960-16,960] neutrophils, 81.2% of total WBC), median ESR was

106 [IQR 89-120] mm at the first hour, median CRP level was 161 [IQR 128-181] mg/L, median ferritin level was 847 [IQR 400 -917] µg/L, and median percentage of glycosylated ferritin was 14 [IQR 10-26]% **(Table 2)**. One patient had a systemic monocyclic evolution, six had a systemic polycyclic evolution (of which two showed a more chronic articular phenotype during later evolution), and one showed a chronic articular evolution from the outset, after an initial systemic flare. Mean number of systemic flares was 2.8±1.9 (SJIA: 2.0±1.0; AOSD: 3.4±2.1) **(Table 2)**.

Complications occurred in three patients (minimal pericarditis without hemodynamic consequences in one; pleural effusion, constrictive pericarditis and myocarditis in one; macrophage activation syndrome in one) **(Table 2)**.

SpA-related features

The features are reported in **Table 3** and **Supplementary Table 1**. At the time of onset of SpA manifestations, SJIA/AOSD was in complete remission (under treatment) in two patients and in partial remission despite ongoing therapy in five **(Table 3).** In the patient showing SpA before AOSD manifestations, the peripheral SpA was in partial remission under MTX at the time of AOSD symptom onset.

No patients had a family or personal history of SpA. Two and five patients had a family and personal history of skin psoriasis, respectively. However, we found no personal or family history of uveitis or IBD.

At onset of SpA-related symptoms, mean TJC (data available for seven patients) was 8.2±7.5, SJC (data available for seven patients) was 4.1±4.3, and enthesitis count (data available for eight patients) was 0.8±1.4. Five patients had skin psoriasis at onset or during the evolution of

SpA manifestations. Three patients had inflammatory backpain and/or pygalgia, and mean CRP level was 34.3±62.2 mg/L. The HLA-B27 status was negative in all patients.

Besides the less-specific wrist arthritis, radiological features of Spa were observed **(Figures 1 and 2, and Supplementary Table 1)**: uni- or bilateral sacroiliitis suggestive of SpA (n=3); bilateral coxitis (n=1); involvement of the fingers with marginal erosions, bone sclerosis, ankylosis and joint destruction following a "PsA-like" pattern on MCP, PIP and DIP joints (n=2); multifocal erosive spondylodiscitis suggesting Andersson lesions (n=1); and erosive and inflammatory arthritis of the left sternoclavicular joint (n=1).

Three patients fulfilled the ASAS criteria for axial SpA, two the ASAS criteria for peripheral SpA, and seven the ESSG criteria **(Table 3**). Four patients fulfilled the CASPAR criteria for PsA; in a fifth patient (case 7) these criteria were almost reached **(Table 3)**. However, this same patient fulfilled the SAPHO criteria.

Response to therapies

Treatments received and their efficacy are summarized in **Table 4**. One adult (case 6) reached complete remission under secukinumab (after loss of efficacy to anakinra and MTX) after the SpA onset. NSAIDS had to be added to anakinra to reach remission in patient 7 after the onset of SpA manifestations.

In the three paediatric patients, SpA symptoms responded completely to TNF inhibitors in two patients; the response was partial in the 3rd patient who was finally lost to follow-up.

Estimation of SpA prevalence

The three paediatric patients with a diagnosis of SpA were from the same centre in which 30 SJIA patients were followed actively. This represented an estimated prevalence of 10% (95%

CI [2.11-26.53]). For the adults with a diagnosis of SpA, four were from one centre and one was from another centre. The active file of AOSD patients followed in both centres represented 76 patients, for an estimated prevalence of 6.58% (95%CI [2.17-14.69]).

Discussion

Although SJIA/AOSD and SpA are quite heterogeneous conditions genetically, pathophysiologically, and clinically, to our knowledge, this is the first case series reporting the association between SOJIA/AOSD and SpA. Only three other publications indexed in PubMed reported this phenomenon. One is a single case in a 31-year-old African patient, followed for 10 years for axial spondylitis, who showed a single systemic and febrile flare fulfilling Yamaguchi and Fautrel criteria, with favourable evolution under corticosteroid treatment (23). Another publication also reported a single case of AOSD in a 21-year-old Korean man with a previous diagnosis of AS and Crohn's disease (24). The last publication reported four Turkish patients who presented a febrile syndrome fulfilling Yamaguchi criteria at the onset of axial SpA (25). However, unlike the previous publications or the patients in our sample, there was no time interval (or at least no time interval reported) between the onset of SpA and AOSD manifestations. Therefore, the cases exhibited febrile onset of SpA rather than two associated diseases, and how many of those patients could be classified as having AOSD is unknown. Additionally, there are few worldwide case descriptions of AS presenting high fever, but these reports lacked any information on rash or serum ferritin levels and the cases did not fulfil SJIA or AOSD classification criteria (26,27). Finally, we found an old report of a series of 202 cases with juvenile RA: probable or definite sacroiliitis was detected in 24% of the patients, with no other symptoms suggestive of SpA (28).

Although there is a potential referral bias in our report, the higher prevalence of SpA in our SJIA and AOSD cohorts than in the adult French general population (estimated at about 0.3%, 95% CI [0.17-0.46] (29) and 0.016% to 0.15% in the paediatric general population of industrialized countries (30)), suggest a possible pathophysiological link between these two entities.

The pigeonholing of Still's disease has been an issue since Bywaters first described the disease in adults (31). Until today, three evolution patterns had been described: monocyclic course (self-limited or reaching drug-free remission after the initial treatment), recurrent or polycyclic course (characterized by disease relapse after a few months or years under immunomodulatory treatments or after discontinuation) and chronic and progressive course (involving continuous inflammation responsible for chronic and frequently erosive joint involvement with regular systemic flares) (1,3,4,31). However, these patterns are mainly based on case series of limited size and not robust epidemiological studies. Furthermore, they were mainly established a long time ago, before the era of the biological treatments. The evolution toward SpA in our patients opens up new avenues of reflection. The current perception of Still's disease (SJIA and AOSD) tends to consider this disease as the archetype of non-familial, or sporadic, systemic autoinflammatory disorders (1). Similarly, current insights argue for an autoinflammatory rather than autoimmune origin in SpA (14). In fact, since the early 2000s, the classification of immune-mediated inflammatory disorders has been refined, and rather than a two-tiered classification, with autoimmunity on one side and autoinflammation on the other, which might be applied for some rare monogenic autoimmune or autoinflammatory diseases, these categories represent in reality a continuum (2,9,18). Hence, besides the "classical" extra-articular manifestations of SpA, such as uveitis, skin psoriasis or IBD, which can be considered associated diseases (14), other associations have been described in autoinflammatory patients: SpA and Behçet's disease (32,33), SpA and FMF (34), SpA and

sarcoidosis (35), SpA and hidradenitis (36), pyoderma gangrenosum and IBD or inflammatory arthritides (37). Similarly, an association between AOSD and other inflammatory diseases has been reported: Crohn's disease (38), sarcoidosis (39) and neutrophilic urticarial dermatosis (40).

The main issue is whether the cases we observed correspond to an overlap or more probably a shift. SJIA/AOSD was in partial remission (under treatment) in most of our patients at the onset of SpA manifestations. In the patient showing SpA before AOSD manifestations, the SpA was in partial remission under MTX at the onset of AOSD symptoms. That the underlying first disease was not in complete remission at the onset of manifestations of the second disease might indicate a state of low-grade inflammatory process that might have decompensated ultimately. Indeed, the sequence first started in most of our patients with the SJIA/AOSD manifestations and then SpA features. Yet, the main cytokines produced during SJIA/AOSD flares are IL-1β, IL-18 and IL-6 (1,41). Along with IL-23, these cytokines participate in the differentiation of T helper 17 (Th17) cells (42). These cells have an important role in the peripheral form of SpA and PsA. Moreover, increased IL-17 level in SJIA/AOSD has been reported (1,41), and IL-17 is the determining cytokine in the axial form of SpA (42). The "cytokine burst" during an SJIA/AOSD flare may trigger, via an overexpression of these cytokines, a form of SpA, thus indicating a shift rather than an overlap in disease. Moreover, IL-17 is also involved in the recruitment of neutrophils, thus contributing to the maintenance of the inflammatory phenomenon (43). This situation could also explain in part the difficulty in treatment for some of these patients. Indeed, secukinumab, an anti-IL-17 monoclonal antibody used for SpA, was required to reach remission in patient 6. In this patient, AOSD was in complete remission (under anakinra, an anti-IL-1 biological agent) at the onset of SpA manifestations. This observation could suggest a shift towards a "type 3 immunity" profile, with a predominance of IL-17 level as compared with the other cytokines involved. Indeed, anti-IL-6 and anti-IL-1 agents have not shown efficacy in SpA. The fact that the life-threatening

complications (pericarditis, myocarditis, pleural effusion, macrophage activation syndrome) all occurred before the onset of SpA also argues for a phenotype shift rather than an overlap, since SpA are at less risk of visceral complications than SJIA/AOSD (1,44).

All these elements suggest that the manifestations of SpA should be differentiated from the forms of Still's disease with chronic articular damage. It pleads for another disease with a common ground or mechanism. Consistent with our findings and hypotheses, several works report the possibility of a switch of phenotype in autoinflammatory disorders, suggesting that autoinflammation may turn into "autoimmune inflammation" (45). Prolonged elevation of IL-1β and IL-18 levels in patients with persistent autoinflammatory states can also affect T-cell differentiation (46,47). Auto-immune animal models show that IL-1 signalling in T cells results in the induction/differentiation of Th17 cells and Th17-mediated immunopathology, when synergizing with IL-6 and IL-23 activation (48). This Th17 polarization in IL-1–mediated disease can occur in patients with FMF (a monogenic systemic auto-inflammatory disorder) (49). Spondyloarthritis, mainly sacroiliitis, eventually develops in up to 3% of the patients with FMF (50). Besides this link with SpA, FMF also showed a strong association with MHC class I-related diseases, referred to as "MHC-I- opathy": Behçet's disease, psoriasis, Crohn's disease and ulcerative colitis (33,34).

The fact that HLA-B27 testing was negative in all our patients can seem confusing at first. However, the prevalence of HLA-B27 positivity varies according to the series reported and according to the subgroups of SpA. For example, the reported frequency of HLA-B27 positivity in studies ranges from 80% to 95% in AS patients but only 20% to 50% for those with PsA (51). In our study, almost half of the patients (n=4) fulfilled the CASPAR criteria for PsA, and in a fifth patient, these criteria were almost fulfilled. However, this same patient fulfilled the SAPHO criteria, which is classically HLA-B27–negative spondyloarthropathy (21). Furthermore, HLA-

B27 positivity explains only 20% of the genetic risk associated with the disease, and there are several polymorphisms in loci associated with the axial form of the disease that induce susceptibility. Moreover four of these genes are immune system genes belonging more to the innate arm of the immune system: IL-6R, IL-1R2, IL-12B and IL-23R (42). In the McGonagle and McDermott classification, SpA is located at the innate–adaptive immune interface (18). Also, this link with the innate immune system is even more interesting in JIA, which can be classified as a polygenic autoimmune disease, some forms of which are phenotypically very close to the SpA spectrum. Also, in their concept of "MHC-I-opathy" mentioned above, McGonagle et al. highlight the differential immunopathology among the different entities belonging to the group of spondyloarthropathies, some being not linked to HLA-B27 but rather to other MHC-I genes (33). A Japanese team reported a family with AOSD in a young man and PsA in his father, both being HLA-B39–positive, which suggests that this positivity likely played an important pathogenic role (52). However, we were not able to obtain the status for this precise HLA allele or for the other MHC-I or II genes in our patients.

The main study limitation is the loss of some clinical and paraclinical information, which is inherent to all retrospective observational studies (53). However, this loss might have had minor importance in this case, because most data allowing for drawing clinical conclusions, especially for the diagnosis of the different clinical pictures, were available. Furthermore, the mean follow-up was long (10.8±6.0 years), which allowed for an exhaustive description of the clinical, biological and radiological evolution for each patient over time. Serum ferritin levels were not available for all patients at disease onset, which may be explained by the lack of information on dosage at baseline (retrospective study design). Serum ferritin levels were not available for all patients at disease onset. This situation can be explained in part by this biological parameter not

being initially assessed in all patients owing to the retrospective study design. In some other patients (cases 3 and 8), serum ferritin levels were assessed but were not elevated at baseline, which may represent an expression of disease heterogeneity. This heterogeneity may be partly related to different serum cytokine levels: recently IL-18 level was found positively correlated with ferritin level and IL-37 level correlated better with CRP level (54). Increased serum ferritin level, although important for SJIA/AOSD diagnosis, is only one of the suggestive findings of the disease and the classification criteria (6,55). Importantly, follow-up and data collection at the time of subsequent relapses ensured that patients had initially shown Still's disease. An important limitation is the lack of some genetic and cytokine characterization of our patients, which does not allow us at this stage to draw strong conclusions about our hypothesis of a pathophysiologic link between SJIA/AOSD and SpA. However, the present paper may constitute a first step that could guide future biological investigations. Another limitation is the difficulty, even the impossibility, to determine whether treatment could have affected the shift of phenotypes from AOSD toward SpA manifestations. Most of the patients were under anakinra therapy at the first manifestations of SpA/PsA, which might only reflect the importance of this molecule in the current therapeutic strategies. Indeed, along with IL-6 blocking agents, anakinra is one of the key drugs used for treating SJIA/AOSD (1). Likewise, most of the patients had received prednisone and MTX, which are first-line treatments in many rheumatic diseases.

In conclusion, the association of SJIA/AOSD and SpA in the same patient suggests a possible pathophysiologic link between the two entities, which requires further investigation. If a shift is confirmed, the AOSD phenotypes may need to be reshuffled.

Table 1. General characteristics of eight patients with systemic-onset juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD) eventually showing spondyloarthritis (SpA).

	SJIA			**AOSD**				
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8***
Sex (female/male)	M	M	F	M	F	M	F	M
Ethnicity	Caucasian	Caucasian	Caucasian	African	Caucasian	Caucasian	Caucasian	Caucasian
Current age, (years); *date of birth (month/year)*	14 *(06/2006)*	26 *(03/1995)*	15 *(10/2005)*	19 *(04/2002)*	47 *(09/1974)*	47 *(08/1973)*	54 *(10/1966)*	57 *(09/1963)*
Age at onset of SJIA/AOSD symptoms (years)	0.8 *(10 months)*	6	6	16	39	28	46	48
Age at onset of SpA symptoms (years)	10	13	11	16.2	42	40	51	37
Duration of follow-up (years)	10 *(then lost to follow-up)*	20	9	3	7	20	8	10

**This patient first showed SpA symptoms, before AOSD was diagnosed 11 years after the diagnosis of SpA*

Table 2. SJIA and AOSD data for the eight patients at disease onset and during the disease evolution.

	SJIA			AOSD				
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**
Temperature >39°C	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Arthralgia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Arthritis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sore throat	No	Yes	Yes	Yes	Yes	Yes	No	No
Skin rash	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Lymphadenopathy	No	Yes	Yes	Yes	Yes	No	Yes	No
Hepatomegaly	No	No	No	Yes	Yes	No	No	No
Splenomegaly	No	No	No	No	Yes	No	No	No
Elevated WBC*: yes/no (rate in /mm^3, if available)	Yes (25,700)	Yes (22,000)	No (8,340)	Yes (16,180)	Yes (21,000)	Yes (but levels NA)	Yes (but levels NA)	Yes (17,000)
Elevated neutrophil count: yes/no; rate in /mm^3 (% of WBC)	Yes; 16,960 (66%)	Yes; 17,600 (80%)	No; 4,170 (50%)	Yes; 13,960 (86%)	Yes; 20,000 (95%)	Yes (but levels NA)	Yes (but levels NA)	Yes; 14,960 (88%)
Elevated CRP level >5 mg/L: yes/no (rate in mg/L)	Yes (186)	Yes (180)	Yes (163)	Yes (160)	Yes (250)	Yes (but levels NA)	Yes (68)	Yes (148)
Elevated liver transaminase levels	Yes	No	No	No	No	No	No	No

Elevated ferritin level (NR 30-400 µg/L): yes/no (rate in µg/L if available)	Yes (5420)	NA	No (235)	Yes (783)	Yes (902)	Yes (but levels NA)	NA	No (151)
Low ferritin glycosylated fraction <20%: yes/no (rate in % if available)	Yes (18%)	NA	Yes (18%)	No (29%)	Yes (11%)	NA	NA	No (40)
Positive rheumatoid factor	No	No	No	No	No	No	No	No
Positive ACPA yes/no	No	No	No	No	No	No	No	No
Positive ANA yes/no	Yes (1/320, unspecific)	No	No	No	No	No	No	No
Evolution mode*	Chronic articular	Systemic polycyclic, then chronic articular	Systemic polycyclic, then chronic articular	Monocyclic	Systemic polycyclic	Systemic polycyclic	Systemic polycyclic	Systemic polycyclic
Number of systemic flares	1	2	3	1	7	3	3	3
Complications during SJIA/AOSD evolution	No	No	Minimal pericarditis	Pleural effusion, constrictive pericarditis and myocarditis	MAS	No	No	No
Fulfils Still's disease criteria (yes/no)								
• Yamaguchi and Fautrel criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
• ILAR criteria	Yes	Yes	Yes	Yes	-	-	-	-

* Normal rate: 4,000-10,000/mm^3

ACPA, anti-citrullinated protein antibodies; ANA, anti-nuclear antibodies; CRP, C-reactive protein; MAS, macrophage activation syndrome; NA, not available; NR, normal rate; WBC, white blood count; ILAR, International League of Associations for Rheumatology

*The evolution modes were classified as follows (1,3,4): monocyclic, when the course was self-limited or included drug-free remission; systemic polycyclic, when the course was characterized by AOSD relapse following either months or years of immunomodulatory treatment or therapy discontinuation; chronic articular, when the chronic and progressive course involved continuous inflammation that was responsible for chronic erosive joint involvement with regular systemic flares.

Table 3. SpA-related features.

	SJIA			AOSD				
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**
SJIA/AOSD status at time of SpA symptoms onset (active/partial remission/complete remission)	Partial remission (dependent on 5-10 mg/day prednisone)	Partial remission (under PDN and MTX)	Partial remission (under TCZ)	Partial remission (under PDN + MTX)	Partial remission (under anakinra)	Complete remission (under anakinra)	Complete remission (under anakinra)	Partial remission of the SpA symptoms at AOSD onset* (under MTX)
SpA data at onset								
Arthralgia: yes/no (tender joint count when available)	Yes (22)	Yes (14)	Yes (6)	Yes (8)	Yes (NA)	Yes (5)	No (0)	Yes (2)
Arthritis: yes/no (swollen joint count when available)	Yes (10)	Yes (10)	No (0)	Yes (2)	Yes (NA)	Yes (5)	No (0)	Yes (2)
Enthesitis: yes/no (enthesitis count when available)	No (0)	Yes (4)	Yes (2)	Yes (1)	No (0)	No (0)	No (0)	No (0)
Inflammatory backpain and/or buttock pain	No	No	Yes	Yes	No	No	Yes	No
Family background with skin psoriasis	No	No	No	No	No	No	Yes	Yes
Personal medical history of skin psoriasis	Yes	No	No	No	Yes	Yes	Yes	Yes (palmoplantar pustulosis)
Current skin psoriasis	Yes	Yes (nail dystrophia)	No	No	Yes	Yes	No	Yes (plantar pustulosis)

Acne	No	No	No	No	No	No	Yes *(+sebaceous and pilonidal cyst)*	No
CRP level at onset of SpA/PsA clinical features (in mg/L)[i]	10	< 5	< 5	183	25	<5	< 5	48
HLA-B27 status	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
SpA criteria fulfillment								
ASAS criteria – axial spondylarthritis	No	No	Yes	Yes	No	No	Yes	No
ASAS criteria – peripheral spondylarthritis	No	Yes	No	No	No	No	No	Yes
ESSG criteria for spondylarthritis	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CASPAR criteria for PsA	Yes	No	No	No	Yes	Yes	No*	Yes

NA: precise data (e.g., swollen or tender joint count) not available

[i]Normal CRP level < 5 mg

*The patient presented axial involvement and 2 of 3 criteria needed (personal history of psoriasis and negative for rheumatoid factor)

PsA, psoriatic arthritis; ESSG, European Spondyloarthropathy Study Group; MTX, methotrexate; PDN, prednisone; TNFi, TNF inhibitor.

Complete remission under treatment was defined as the absence of any clinical and biological sign of the disease, i.e., the disappearance of fever, arthralgia and arthritis, myalgia, sore throat, rash, adenopathy, hepatosplenomegaly, and the normalization of blood count, ESR, CRP and serum ferritin levels.

Partial remission corresponded to some improvement noted by the physician in charge of the patient, but some systemic, articular, or biologic features persisted after treatment start.

Treatment failure was considered if SJIA/AOSD symptoms remained mainly unchanged during treatment.

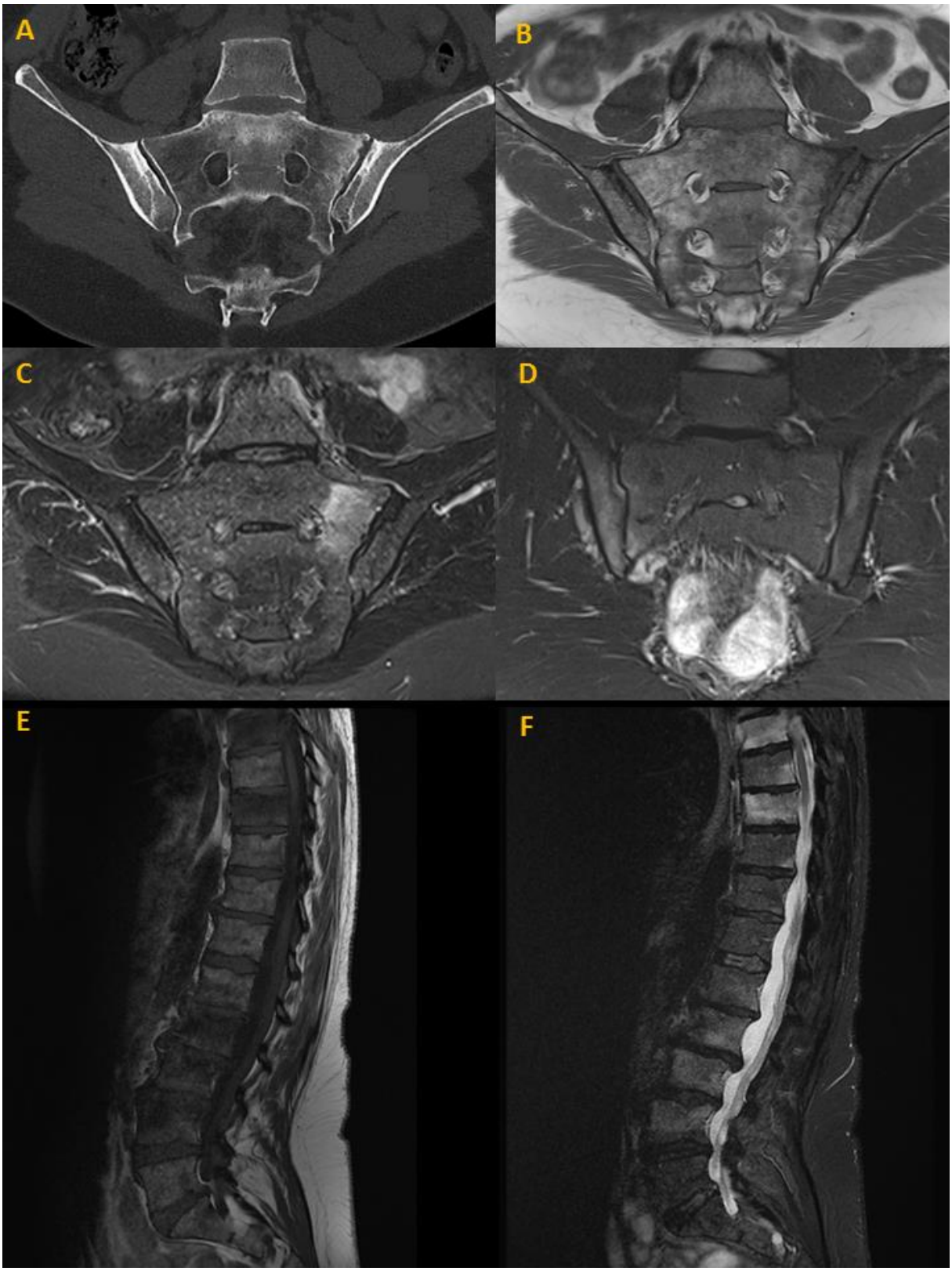
Table 4. Treatments and efficacy.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Treatment prescribed for SJIA or AOSD manifestations	Ig (F) PDN (PR) IFX (PR) ETN (PR) MTX(PR) CANA (F) TCZ (PR)	PDN (PR) PDN + MTX (PR)	PDN (PR) CANA (F) TCZ (PR)	PDN + MTX (PR)	PDN + MTX (PR) ANA (PR) TCZ (skin allergy) Anakinra (PR)	MTX + PDN (CR, then LoE during PDN decrease) MTX + ETN (CR, then relapse) MTX+ ADA (F) MTX + IFX (F) MTX + ABA (F) MTX + ANA (CR) -> switch for ANA only (CR)	PDN (PR, then loE during PDN decrease) ANA (CR)	**This patient first developed SpA manifestations and was successively treated with:** NSAIDs (F) SZP (PR) MTX (PR and persistent elevation of the CRP)
Treatment taken when first manifestations of SpA/PsA noticed	PDN (PR)	PDN + MTX (PR)	TCZ (PR)	PDN + MTX (PR)	ANA (PR)	ANA (CR)	ANA (CR)	**This patient first developed SpA manifestations. At onset of AOSD manifestations, he was treated with:** MTX
Treatment prescribed after the diagnosis of SpA or PsA	ETN (PR) then lost to follow-up	PDN + MTX + ETN, then ETN alone (CR)	ADA (CR)	PDN + MTX (CR, allowing PDN and MTX discontinuation; patient in CR without treatment more than 6 months after treatment discontinuation)	PDN + MTX + IFX (PR, then systemic allergic reaction to IFX) PDN + MTX + ANA (PR)	MTX + ANA (CR) -> switch for MTX only (CR, then LoE) MTX + SECU (CR)	ANA + NSAIDs (indomethacin) : CR for AOSD manifestations, but dependent on NSAIDs for SpA manifestations Possible discontinuation of NSAIDs after 6 months of treatment (CR under ANA alone)	**Treatment prescribed after the diagnosis of AOSD was made** MTX + PDN (PR) MTX +ANA (CR, then relapse) MTX + apremilast (F) MTX + TCZ (CR)

ABA, abatacept; ADA, adalimumab; ANA, anakinra; CANA, canakinumab; CR, complete response; ETN, etanercept; F, failure; IBP, inflammatory back pain; IFX, infliximab; Ig, immunoglobulins; LoE, loss of efficacy; MTX, methotrexate; NSAIDs, non-steroidal anti-

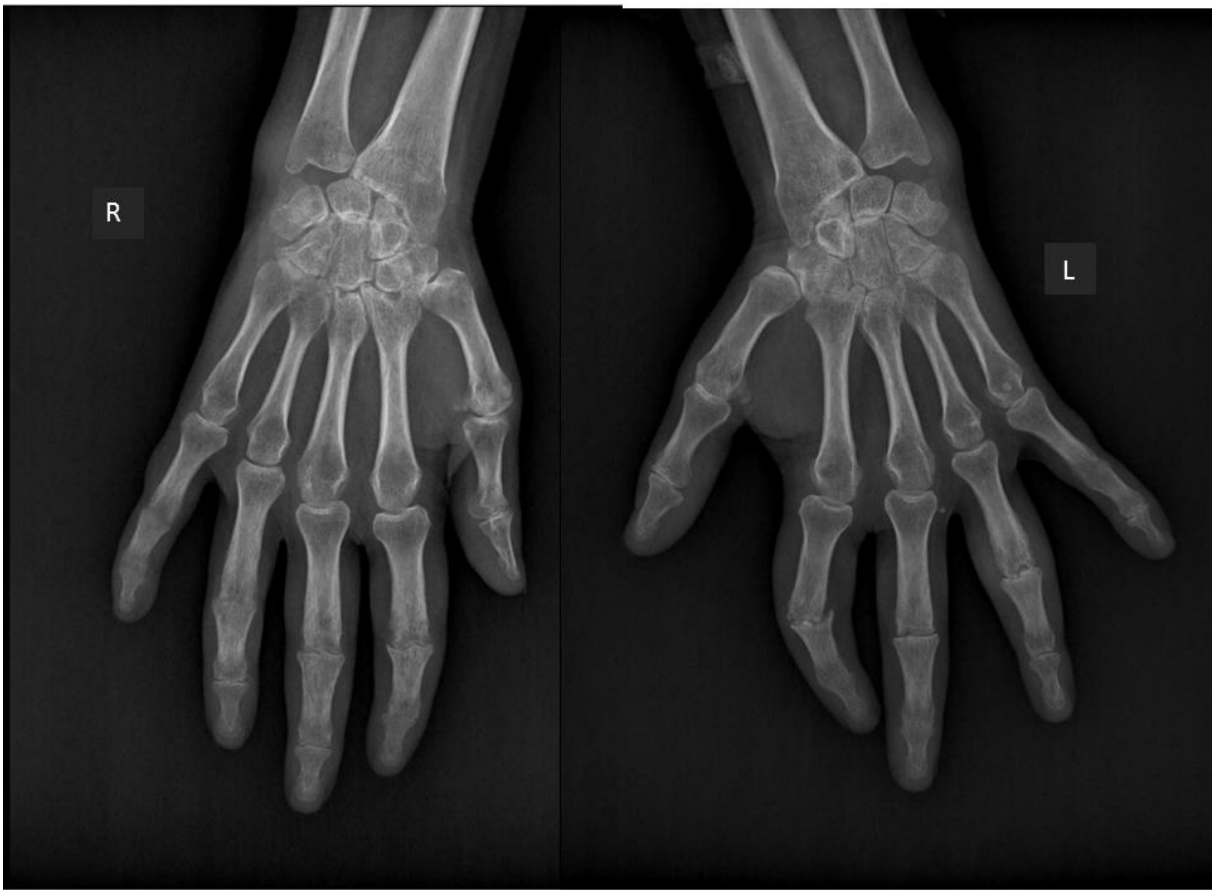
inflammatory drugs; PDN, prednisone; PR, partial response; PsA, psoriatic arthritis; IR, insufficient response; SECU, secukinumab; SpA, spondylarthropathy; SZP, salazopyrin; TCZ, tocilizumab

Figure 1. Axial SpA-related radiological features



A. Left sacro-iliitis (bone erosions on the sacral side at the superior aspect of the joint, widening of the joint space, bone sclerosis) on CT scan, coronal plane (case 7).
B. Same patient (case 7), T1-weighted MRI sequence, coronal plane showing the same erosions and the widening of the joint space.
C. Same patient (case 7), T2-STIR MRI sequence, coronal plane, showing inflammatory lesions, with extended bone-marrow oedema on the sacral side of the joint.
D. Bilateral sacroiliitis, with sub-chondral T2 hypersignal more pronounced on the right side (case 4, T2-STIR MRI sequence, coronal plane)
E. Erosive, inflammatory spondylodiscitis (Andersson lesions) of thoracic spaces 7 to 10 and lumbar vertebrae spaces 1 to 4 with hyposignal and erosions of the endplates on a T1-weighted MRI sequence (case 7).
F. Same patient (case 7), same lesions with hypersignal of the endplates on a T2 STIR sequence (inflammatory lesions). Some of the vertebrae have annulus corner-bone oedema posteriorly, especially at T8 and T10. These are more typical of SpA than diffuse vertebral body bone oedema.

Figure 2. “Psoriatic arthritis-like” involvement of the hands



Radiographs of the hands and wrists of the patient 5 who fulfilled CASPAR criteria for psoriatic arthritis (PsA).

Wrist arthritis with bilateral radiocarpal, mediocarpal and carpometacarpal erosions and joint space narrowing. Characteristic involvement of the fingers with polyarthritis of asymmetrical distribution, marginal erosions associated with bone proliferation (4^{th} right and 2^{nd} left PIP), articular destruction with a “pencil-in-cup” pattern and joint subluxation (2^{nd} left PIP), distal involvement of the DIPs, involvement of all joints of a same finger (especially 2^{nd} and 5^{th} right fingers, 3^{rd} and 5^{th} left fingers), ankylosis of several PIP and DIP joints.

DIP, distal interphalangeal; PIP, proximal interphalangeal.

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