Original Research *Highlight article*

Acute joint swelling in psoriatic arthritis: Flare or "psout"—A 10-year-monocentric study on synovial fluid

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Impact Statement

Recently, Felten and colleagues proposed the term "psout" to indicate the concurrence of psoriatic arthritis (PsA) and gout as a novel overlap syndrome, at the boundary between inflammatory and metabolic rheumatism. Given the importance of synovial fluid (SF) analysis in Rheumatology, we analyzed the SF in a cohort of 213 patients with PsA to describe the acute joint swelling in PsA patients and determine whether it is a flare or an acute episode of gout ("psout") involving the role of urate crystals. Almost 10% of these PsA patients with acute joint swelling present hyperuricemia. Despite that, monosodium urate crystals are rarely found (2.4%) in SFs of our cohort of patients. The results reported for the evaluation of the crystals and the degree of inflammation do not seem conclusive to ascertain the etiology of acute joint swelling; however, they are a stepping stone to further study, such as SF cultures.

Abstract

Psoriatic arthritis (PsA) is a multifaceted inflammatory disease associated with psoriasis that can affect peripheral joints, entheses, and the axial skeleton with a variable clinical course. Acute episodes of joint swelling in PsA patients can have different causes and require specific treatments. We aimed to describe the acute joint swelling in PsA patients via synovial fluid (SF) analyses, assessing in particular the presence of pathogenic crystals, to determine whether it is a flare or an acute episode of gout ("psout") during the course of the disease. This retrospective study was based on the results of SF analysis of samples collected from unselected adult PsA patients referred to our clinic for acute joint swelling. Demographic characteristics, disease involvement, laboratory findings on SF, and treatment options were recorded and reviewed. Among 5,478 SF samples analyzed in a 10-year time span, 213 complete SF records from PsA patients were evaluated. Overall, after adjustment for the degree of synovial inflammation, significant differences were observed in term of sex ($p = 0.0017$) and ongoing therapy ($p = 0.0246$). Non-inflammatory SFs, indeed, were mainly described for female PsA patients under therapy. Regarding serum uric acid levels, there were 19/213 (8.9%) PsA with hyperuricemia (HU), who were older, mostly male, patients with mild articular involvement and rare pathogenic crystals in their SF. Although it is known that the risk of gout is higher among patients with PsA ("psout"), monosodium urate crystals were reported only in 5/213 SFs (2.4%) of our cohort and in 2/19 SFs (10.5%) of HU PsA patients. Moreover, hyperuricemia seems not to modify the SF features in PsA patients. This study results seem to suggest that the convergence of gout and PsA, involving the role of urate crystals, is a more intricate relationship, which needs further insights to be unraveled.

Keywords: Synovial fluid, psoriatic arthritis, "psout", hyperuricemia, crystals, acute joint swelling

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Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory arthropathy associated with psoriasis, with a prevalent peripheral joint involvement, more often associated with peripheral enthesitis, psoriasis, and dactylitis.[1] Inflammation at joints and entheseal sites results in the development of an acute synovial swelling, followed by bone and articular damages.[2,3] Treatment focuses on controlling inflammation to prevent joint pain and disability using first nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids, then disease modifying drugs (DMARDs) that can slow the disease progression. Effective biologics and small-molecules drugs, including TNF, IL-12/23, and IL-17 inhibitors, are useful in case of failed response to traditional treatments.[4–7]

The management of PsA can be challenging mainly due to lack of specific biomarker[8] and the presence of several comorbidities associated with the disease, including cardiovascular disease, obesity, hypertension and metabolic syndrome, hyperuricemia, malignancy, liver and kidney diseases, and infections.[9]

Hyperuricemia (HU), described as elevated serum uric acid levels, resulted threefold greater in psoriatic patients than in the general population.[10] Although HU is essential

for monosodium urate (MSU) crystal formation, not all hyperuricemic individuals develop gout.[11,12] The mechanism behind the interplay between HU and PsA is not fully understood. Increased serum uric acid levels in PsA may stem from the elevated cutaneous cell turnover, as well as the known systemic inflammation state associated with PsA.[13,14] Recently, Felten and colleagues proposed the term "psout" to indicate the concurrence of PsA and gout as a novel overlap syndrome, at the boundary between inflammatory and metabolic rheumatism.[15] It has been established that biomechanical forces on tendons and adjacent synovial tissues may trigger an inflammatory response that attracts inflammatory cells, thus resulting tendon inflammation and swelling.[16] Clinicians can take advantages of the diagnostic value of synovial fluid (SF) analysis, which has long been recommended to help distinguish between inflammatory and non-inflammatory forms of arthritis.[17] SF analysis is indeed one of the most useful laboratory procedures for the differential diagnosis of joint diseases. SFs analysis is mandatory to identify MSU and calcium pyrophosphate (CPP) crystals and clearly differentiate crystal-induced arthritis.[18] In our previous work, we observed that pathogenic crystals can be detected more frequently than expected in SF from joint diseases with a previous established diagnosis.[19] Concerning PsA patients, the prevalence of MSU and CPP crystals observed in their SF was estimated to be 3.34% and 3.82%, respectively.[19] Given that crystal diseases are common in the general population, it may be challenging to determine whether an episode in PsA patients presenting with acute monoarthritis is due to PsA itself or to MSU crystals. A PsA flare, indeed, displays escalation of symptoms and signs across multiple domains.[20]

We aimed to describe the acute joint swelling in PsA patients to determine whether this would be a flare or an acute attack of gout during the course of the disease. Identifying the presence of pathogenic crystals would help to avoid misclassification of the flare.

Materials and methods

Collection of SF and analysis

We analyzed the data from 5,478 SF samples collected from outpatients referred to the Diagnostics Centre for Synovial Fluid, Rheumatology Unit, Padova University Hospital (Italy) between January 2010 and December 2020. The inclusion criteria were (1) patients with a well-defined PsA diagnosis according to the Classification criteria for Psoriatic Arthritis (CASPAR);[21] and (2) PsA patients who underwent arthrocentesis for an acute episode of swollen and painful joints. Arthrocentesis was performed with or without ultrasound (US) guidance depending on the anatomical site.[22]

SF analyses were performed by three trained specialists (PG, OF, AS) using conventional techniques. Total white blood cell (WBC) count was determined using a Bürker counting chamber, and differential cell counts were assessed with pre-stained slides for cell morphology (Testsimplets® Waldeck, Biosigma). WBC and differential (% PMN) cell counts allow to determine the degree of inflammation in SF: no inflammation (<200–2,000 WBC/mm^3), moderate inflammatory SF (2,000–5,000 WBC/mm^3), and severe inflammation (5,000–50,000 WBC/mm^3).[23]

Crystals were identified under a compensated polarized light microscope, which allows to identify their different morphology and birefringence. MSU crystals present the characteristic needle shape and intense birefringence with negative elongation. CPP crystals are instead recognized by their rod or rhomboidal shape and weak birefringence with positive elongation.

The study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the local Ethics Committee (Protocol n. 0039872, 20/07/2015). All patients provided written informed consent.

Clinical and biochemical data

Demographic information (age, sex, disease duration), disease characteristics (axial and/or peripheral involvement), uric acid level, and treatments choices (stable doses of NSAIDs and steroids, synthetic and/or biologic disease modifying drugs) were collected. Serum uric acid (SUA) level was assessed the same day of the arthrocentesis and HU was defined by SUA > 6 mg/dL.[24] Data pertaining to important risk factors for HU (e.g. body mass index [BMI], diet) were not available due to the retroactive nature of our study.

Statistical analysis

All variables were reported as median ± standard deviation (SD), while the demographic variable and SF characteristics were reported with descriptive statistics. To assess the differences between groups subdivided according to the presence of HU, degree of inflammation and treatments, continuous variables were compared using the non-parametric Kruskal–Wallis rank sum test and categorical variable using chi-square independent test. The threshold for a statistically significance difference was set at $p < 0.05$. Graphpad Prism (version 5.01) was used for all statistical analysis.

Results

Among 5,478 samples examined, 482 were from PsA patients. The excluded SF samples were from other arthropathies (osteoarthritis, polymyalgia rheumatica, rheumatoid arthritis, other crystal-induced arthritis) and from more rare rheumatic diseases (vasculitis, adult-onset Still's disease, connective tissue diseases) or with inconclusive diagnosis. An additional 140 SFs were excluded because repeat arthrocenteses in the same patients yielded SF with identical features. Finally, 129 SFs were excluded due to missing clinical information. We ultimately included SF samples from 213 PsA patients with acute joint swelling: 122 (55.9%) males and 94 (44.1%) females with median age of 53.9 ± 13.3 years (Figure 1). Clinical and SF characteristics, therapies, disease duration, and axial and peripheral PsA involvements are reported in Table 1. As regards SF analysis, WBC range was 100 cells per mm^3 to 48,200 cells per mm^3 (Supplementary Figure 1) and SF crystals were found only in 13 (6.1%) samples (Supplementary Figure 2). MSU crystals were present in 5 (2.3%) SFs and CPP crystals in 8 (3.8%); co-existence of MSU and CPP crystals was not observed.

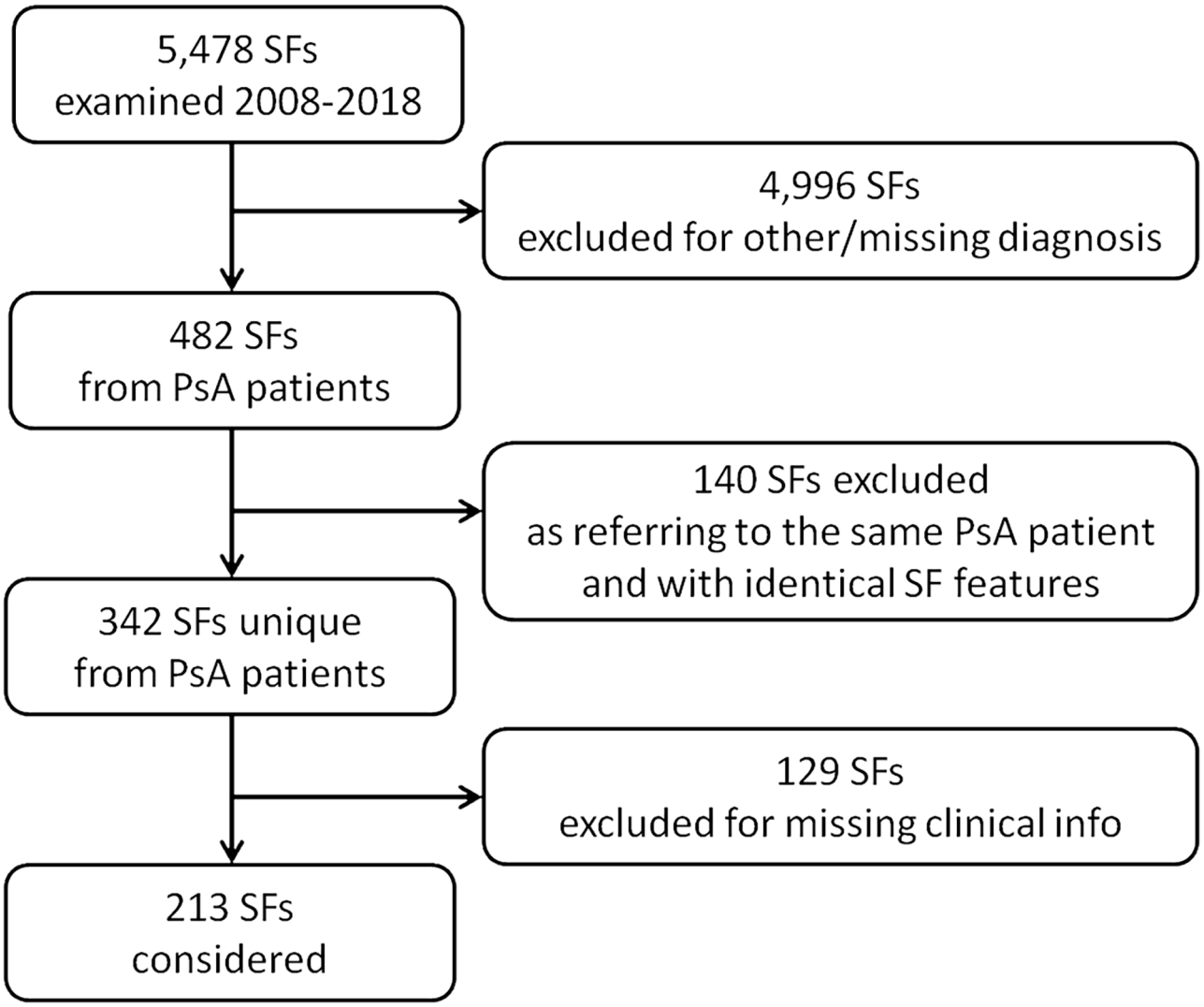

Figure 1. Flowchart of the study.

SFs: degree of inflammation

Table 2 summarized the SF characteristics based on the degree of inflammation, that is, the WBC count as explain in the method section. Seventy-six (35.7%) SFs were considered non-inflammatory based on SF WBC count less than 2,000 per mm^3 (Table 2). Moderate inflammatory SF (WBC range, 2,000–5,000 cells per mm^3) was observed in 30 (14.1%) samples, while severe inflammation (WBC range, 5,000–50,000 cells per mm^3) in 97 (45.5%) samples. Pseudoseptic flares, with a WBC count more than 50,000 cells per mm^3, were not observed in our SFs, even though they can occur in PsA and crystal arthritis. Ten of 213 samples were excluded due to incomplete data on SFs-WBC related to the insufficient amount of fluid for cell count. Significant differences were observed in term of sex ($p = 0.0017$) and ongoing therapy ($p = 0.0246$). Non-inflammatory SFs, indeed, were mainly described for female PsA patients under therapy.

SFs: involved joints

Overall, arthrocentesis was performed in 161 (77.4%) knees, in 22 (10.6%) hand joints (proximal interphalangeal [PIP],

Table 1. Characteristic of the study population at the SF analysis.

PsA patients' characteristics (213 patients)	
Sex, male/female (%)	119/94 (55.9/44.1)
Age, years	53.9 ± 13.3
Disease duration, years	7 ± 7.9
Peripheral PsA (%)	202 (94.8)
Oligoarticular involvement (%)	184 (86.4)
Therapy (%)	189 (88.7)
NSAIDs (%)	66 (31)
Steroids (%)	54 (25.4)
DMARDs (%)	118 (5.4)
Biologics (%)	50 (23.5)
combined DMARDs and biologics (%)	19 (8.9)
SFs characteristics of PsA patients (213 SFs)	
SF Volume, mL	28.8 ± 35.9
SF WBC, cells/mm^3	4,850 ± 8,907.1
SF PMN, %	50.5 ± 31.4
SF crystals (%)	13 (6.1)
CPP crystals (%)	8 (3.8)
MSU crystals (%)	5 (2.3)

SF: synovial fluid; WBC: white blood cells; PMN: polymorphonucleate cells; CPP: calcium pyrophosphate; MSU: monosodium urate. Data are presented as median ± standard deviations or percentages (%).

Table 2. Clinical and SF features of PsA patients based on SF inflammatory pattern.

PsA patients characteristics (213 patients)	Non-inflammatory pattern	Moderate inflammatory pattern	Severe inflammatory pattern	*p* value
No. of PsA patients	76 (35.7)	30 (14.1)	97 (45.5)	
Sex, male/female	32/44	16/14	67/30	0.0017
Age, years	61.3 ± 7.8	47.3 ± 13.1	50.2 ± 14.1	<0.0001
Disease duration, years	7 ± 8.8	7 ± 5.9	7 ± 8	n.s.
Peripheral/axial PsA	69/17	29/8	94/13	n.s.
Mono-/oligoarticular involvement	6/67	4/25	12/83	n.s.
Hyperuricemia (%)	4 (5.3)	1 (3.3)	13 (13.4)	n.s.
Therapy (%)	74 (97.4)	25 (83.3)	84 (86.6)	0.0246
NSAIDs (%)	25 (32.9)	8 (26.7)	28 (28.9)	n.s.
Steroids (%)	21 (27.6)	8 (26.7)	21 (21.6)	n.s.
DMARDs (%)	45 (59.2)	14 (46.7)	52 (53.6)	n.s.
Biologics (%)	10 (13.2)	6 (20)	33 (34)	n.s.
SFs characteristics	Non-inflammatory pattern	Moderate inflammatory pattern	Severe inflammatory pattern	*p* value
SF volume (mL)	14.3 ± 20.0	38.7 ± 43.5	40.3 ± 39.6	<0.0001
SF WBC	616.4 ± 597.7	3,593.3 ± 987.1	13,353.6 ± 9,413.5	<0.0001
SF PMN	24.7 ± 27.1	28.2 ± 19.8	63.6 ± 25.9	<0.0001
SF crystals	10 (13.2)	1 (3.3)	1 (1.0)	0.0029
MSU/CPP crystals	3/7	0/1	1/0	n.s.

SF: synovial fluid; WBC: white blood cells; PMN: polymorphonucleate cells; CPP: calcium pyrophosphate; MSU: monosodium urate; n.s.: not significant. Data are presented as median ± standard deviations or percentages (%).

Table 3. Clinical and SF features of PsA patients with hyperuricemia.

PsA patients ($n = 213$)	Hyperuricemia	Normal uric acid	*p* value
No. of PsA patients	19 (8.9)	194 (91.1)	
Gender, male/female	15/4	104/90	0.0338
Age, years	65.7 ± 10.8	53.0 ± 13.1	0.0011
Disease duration	7.5 ± 6.3	7 ± 8.1	n.s.
Peripheral/axial PsA	19/2	183/37	n.s.
Mono-/oligoarticular involvement	1/18	22/167	n.s.
Therapy (%)	19 (100)	170 (87.6)	n.s.
NSAIDs (%)	10 (52.6)	56 (28.9)	n.s.
Steroids (%)	3 (15.8)	51 (26.3)	n.s.
DMARDs (%)	14 (73.7)	104 (53.6)	n.s.
Biologics (%)	7 (36.8)	43 (22.2)	n.s.
SFs characteristics			
SF volume (mL)	38.7 ± 52.8	27.8 ± 33.8	n.s.
SF WBC	9,116.7 ± 8,378.0	7,054.9 ± 8,956.1	n.s.
SF PMN	59.1 ± 27.2	46.8 ± 31.5	n.s.
SF crystals	3 (15.8)	10 (5.2)	n.s.
MSU crystals	2 (10.5)	3 (1.5)	n.s.
CPP crystals	1 (5.2)	7 (3.6)	n.s.

SF: synovial fluid; WBC: white blood cells; PMN: polymorphonucleate cells; CPP: calcium pyrophosphate; MSU: monosodium urate; n.s.: not significant. Data are presented as median ± standard deviations or percentages (%).

metacarpophalangeal [MCP], and wrists), in 11 (5.3%) elbows, in 7 (3.4%) shoulders, and in 7 (3.4%) foot joints (metatarsophalangeal [MTP] and ankles) (Supplementary Table 1). Five of 213 SF samples were excluded due to incomplete clinical data.

Hyperuricemia

SF samples' characteristics referred to 19 patients with HU are listed in Table 3. Hyperuricemic PsA patients resulted older and with male predominance compared with non-HU patients. Significant difference in HU was observed when patients were grouped by aspirated specific sites ($p = 0.014$), with a higher percentage of HU in patients that presented MCP and wrist effusions (66.7% and 29%, respectively) (see Supplementary Table 1). No significant difference was reported between HU PsA patients and normouricemic patients concerning the presence of MSU and CPP crystals in their SFs.

Discussion

A proper differentiation of the acute joint swelling in PsA patients has scarcely been studied, despite in the literature there are examples suggesting that it could affect patients'

quality of life and treatment options. Discriminating gouty attack from active PsA could help to avoid misclassifications that may lead to unnecessary and even harmful therapies. To investigate this aspect, our study focused on SF characteristics, in particular on the degree of inflammation, the finding of MSU crystals and the hyperuricemic state of the patients.

This study enabled us to highlight the relatively low frequency of gouty attack in our cohort although it is known that the risk of gout is higher among patients with PsA. The prevalence of gout in the Italian general population is 9.1 per 1,000 inhabitants.[25] There is currently no data on the prevalence of gouty attacks in Italian PsA patients in the literature; nevertheless, awareness about the increased incidence of gout in PsA patients, the so-called "psout," is critical.[15] An American study showed that the risk of gout is higher among patients with PsA *versus* patients with psoriasis only (hazard ratio of 4.95 *versus* 1.71).[26]

The importance of discriminating gouty inflammation ("psout") from reactivation of PsA symptoms is linked to the ability of the intra-articular deposition of MSU and CPP crystals to erode joints via pro-inflammatory processes.[27,28] Underlying the crystal-stimulated inflammatory cascade are many complex cellular mechanisms that may lead to an optimized use of existing drugs and the introduction of novel therapeutic strategies.

The acute joint swelling observed in our PsA cohort is characterized by differences in SF inflammation and crystal detection. After adjustment for the degree of synovial inflammation, significant differences were observed pertaining to sex and ongoing therapy. Male gender was linked with more severe SF inflammation. Indeed, gender differences have been reported in the severe forms of spondyloarthritis.[29] In 35.7% of PsA patients, a joint exacerbation without an important inflammatory state has been observed. It is important to remind that 97.4% of these patients were in therapy at the time. The acute joint swelling may have been linked to stressful activities as heavy work or sports that created joint overload. In these patients with non-inflammatory SF, we can assume that joint exacerbation may be under therapeutic control, regardless of the type of therapy. This finding is consistent with previous studies on synovial tissues from PsA patients reporting that long-term treatment correlated with a better management of inflammation (i.e. deactivation of endothelium, fewer blood vessels, and infiltrating immune cells).[30] In these non-inflammatory SFs, we identified the majority of pathogenic crystals (MSU in 3 SFs and CPP in 7 SFs). The three cases of MSU crystals were found in normouricemic patients, but their SF samples also presented a high percentage (50–90%) of polymorphonuclear leukocytes. This finding agrees with the literature[31] on crystal presence in SF with a low-grade inflammation. It is also important to remind that acute gout may occur with normal uric acid levels, particularly in acute episodes.[32] SF analysis for crystals is a simple procedure allowing immediate and confirmed diagnosis of crystal-related arthropathies.[33,34] Interestingly, most pathogenic crystals detected in PsA SFs are CPP crystals. Their significance is unclear despite investigations of possible alterations of biochemical pathways leading to the production of inorganic pyrophosphate in PsA patients.[35,36] Unfortunately, due to the retrospective aspect of this study, it was not possible to investigate whether the presence of CPP crystals could be linked to structural damage to the joints. The presence of MSU crystals is, however, unsurprising given the frequent occurrence of metabolic syndrome in PsA patients[37–40] and the possible involvement of elevated levels of SUA in the development of PsA.[41]

In our cohort, HU was observed in 8.9% of PsA patients, markedly lower than previously reported in the literature—21% by Bruce *et al.*[14] and 32% by AlJohani *et al.*[41] Similarly, an observational study by Prasad *et al.*[42] described elevated serum uric acid levels in 45% of PsA patients. In a recent study, patients with PsA showed a higher incidence of HU than patients with psoriasis alone,[43] and HU has been reported as a possible independent risk factor for PsA in individuals with psoriasis.[44] However, it has to be considered that our data refers to a limited cohort of PsA patients who underwent arthrocentesis for swollen joints. Another possible bias is defining HU at the same day of the arthrocentesis. As during inflammatory situations (such as the gouty flare itself), SUA levels could be lower than after inflammation resolution.

In our patients, HU did not lead to differences in the characteristics of SF (i.e. cell counts, degree of inflammation, and crystal detection). Moreover, despite evidence in the literature suggesting HU might affect severity of clinical manifestations in PsA patients,[45] it did not appear to worsen PsA in our cohort of HU patients. This may stem from an inclusion bias because all our patients were referred for acute swollen joints, therefore with increased disease severity.

We would be remiss not to mention some of the limitations of our study. First, as a medical records review study, some clinical information (e.g. serum inflammatory markers at the time of the flare) were not available. It is however established that a significantly high number of patients with active PsA show normal or near normal C-reactive protein value, unlike other rheumatic diseases.[46] Second, individual BMI and dietary habits which may affect serum uric acid levels—as well as other comorbidities—were not reported at the time of SF collection. Third is the absence of HU assessment at time points other than the flare as a means of correctly identifying hyperuricemic PsA patients.

The reported results about the presence of pathogenic crystals and the degree of SF inflammation could help to avoid misclassification of the flare; however, they do not seem conclusive to ascertain the etiology of the acute joint swelling. The convergence of gout and PsA, involving the role of urate crystals, is a more intricate relationship, which needs further insights to be unraveled.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, interpretation of the studies, and analysis of the data and review of the manuscript; PG and RR designed it; PG, FO, MF, and RR concepted the methodology; ML, AO, and MF collected the SF samples; PG, FO, and AS analyzed the SF samples; PG, AS, AO, and AD performed the data statistics analysis; PG and RR wrote the original draft; and all authors reviewed and edited the manuscript.

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DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

This study was approved by the Ethics Committee for Clinical Practice of the University Hospital of Padova.

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SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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