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Systemic Inflammatory Polyarticular Gout Syndrome - Description of a Previously Neglected Entity

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Abstract

Background: Although systemic inflammatory polyarticular gout syndrome (SIPGS) occurs in clinical practice, only few case reports have yet been published.

Materials and Methods: Retrospective analysis of all consecutive patients between January 2013 and April 2015 with SIPGS, defined by involvement of ≥ 5 joint regions, C-reactive protein (CRP) ≥ 80 mg/l and/or erythrocyte sedimentation rate (ESR) ≥ 80 mm/h, and of age-and gender-matched low-grade inflammatory gout (LIG) patients, with CRP ≤ 80mg/L and ESR ≤ 80mm/h and with at least one joint involved.

Results: Twenty-two of 152 gout patients fulfilled the SIPGS inclusion criteria; 22 age- and gender matched LIG patients were identified. Mean CRP was 172 mg/l (SD ± 84) and 25 mg/l (SD ± 21); mean ESR was 91 mm/h (SD ± 24) and 50 mm/h (SD ± 27) in SIPGS and LIG patients. All SIPGS, but only 12 LIG patients had anemia. Procalciton was always negative. A mean of 10 and 4 joint regions were affected in SIPG and LIG, respectively. All SIPGS patients showed bilateral arthritis, while only 11 LIG patients had bilateral MTP I joint involvement. The interval between symptom onset and admission was 11 and 20 days; while inpatient treatment was 14 and 9.5 days in SIPGS and LIG, respectively. Acute renal failure was common in SIPGS (N=8 vs.1). Non-steroidal antirheumatic drugs (NSAIDs) had to be replaced in all SIGPS patients.

Conclusion: SIPGS patients have bilateral joint involvement and rarely fever. Anemia is common. Normal procalcitonin helps differentiating SIPGS from sepsis. SIPGS may be complicated by renal failure. NSAIDs are ineffective.

INTRODUCTION

Gout is the most common form of inflammatory joint disease with an estimated total prevalence of 2.5% and an incidence of 1.8 per 1000 person years. In recent years, both the prevalence and incidence of gout have increased [1]. Hyperuricemia may lead to asymptomatic articular or extra-articular urate deposition which may be detected by imaging such as ultrasound [2] or dual energy computed tomography (DECT) [3]. The first gout attack most commonly occurs at the first metatarsophalangeal joint followed by an intercritical phase. Progressing intra-and extraarticular urate deposition leads to chronic polyarticular tophaceous gout which is characterized by recurrent gout attacks and in some cases leads to a systemic inflammatory syndrome [4].

Gouty inflammation is due to monosodium urate crystal-induced release of pro-inflammatory cytokines from leukocytes [5]. In mouse models, it has been demonstrated that monosodium urate crystals, serving as danger signals, can activate the intracellular cryopyrin-inflammasome complex, which triggers the release of cytokines and consecutively leads to a sterile systemic inflammatory response [4]. Polyarticular gout with high inflammatory markers seems to be commonly encountered in clinical practice. However, only few case reports have been published until now [6-8]. In a recent case report [6] the authors state that a flare of polyarticular gout may present as pseudosepsis by activating the intracellular cryopyrin-inflammasome complex and that discrimination between sepsis and polyarticular gout may be difficult. However, no case series describing this inflammatory syndrome has been published so far. Knowledge is also limited on the efficacy of antiflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS), colchicine, glucocorticoids (GC) and interleukin-1 inhibitors, like canakinumab, in this particular situation.

Our main objective is to describe the systemic inflammatory polyarticular gout syndrome (SIPGS) in order to identify those patients earlier, and to understand which treatment is best, and which is not, in order to achieve early disease and inflammatory

control for this clinical scenario. For better discrimination of those patients, the same number of age-and gender-matched low-grade inflammatory gout (LIG) patients, who were also admitted to the inpatient unit in the same time interval, were included.

MATERIALS AND METHODS

The medical records of 152 consecutive new patients with gout who were seen between January 2013 and April 2015 in a single tertiary care rheumatology center were reviewed retrospectively. Patients were included in the SIPGS group if they met all of the following criteria: A, definite diagnosis of gout (fulfillment of the ACR / EULAR 2015 gout classification criteria [9]); B, polyarticular involvement, which means at least 5 joint regions affected (1st metacarpophalangeal joints, other metacarpophalangeal joints, ankles, knees, wrists, digits, elbows); C, highly elevated inflammatory markers (C-reactive protein (CRP) ≥ 80 mg/l and/or erythrocyte sedimentation rate (ESR) ≥ 80mm/h) (Table 1).

Age and gender matched LIG patients had to fulfill the following inclusion criteria: A, definite diagnosis (fulfillment of the ACR / EULAR 2015 gout classification criteria [9]); B, involvement of at least one joint region [1stmetatarsophalangeal joints, other metatarsophalangeal joints, ankles, knees, wrists, digital joints (metacarpophalangeal-, proximal or distal interphalangeal joints), elbows)]; C, inflammatory markers (CRP < 80 mg/l and ESR< 80mm/h).

Joint involvement was considered if clinical examination revealed swelling or tophi, or if imaging (ultrasound, DECT or x-ray) showed features consistent with gout in the respective joint regions. Data was analyzed for age, gender, body mass index, visual analogue scales, and laboratory parameters, imaging results, clinical parameters and acute treatment regimens. The study was performed in compliance with the Declaration of Helsinki.

Table 1: Inclusion criteria describing the systemic polyarticular inflammatory gout syndrome.

Criteria	Explanation
1.Definite diagnosis of gout	Fulfillment of the ACR / EULAR 2015 classification criteria for gout
2.Definition of joint involvement	1. Clinical examination : A. Palpable tophi *and/or* B. Joint swelling *and/or* 2. Imaging (ultrasound, DECT or x-ray) A. Ultrasound detection of double contour signd and / or extra- or intra-articular tophi *and/or* B. Crystal detection by DECT Typical gout crystal color pattern *and/or* X-ray detection of tophi and / or presenced of erosions defined as a cortical break with sclerotic margin and overhanging edge at MTP joints
3. ≥ 5 joint regions inflamed Two joint regions are considered positive in case of bilateral involvement.	1. 1st MTP joint 2. Other MTP joints 3. Ankle joints 4. Knee joints 5. Finger joints 6. Wrist joints 7. Elbow joints
4.Raised inflammatory markers	A. CRP ≥80 mg/l *and/or* B. ESR ≥ 80mm/h

Data evaluation and statistical analyses were performed with SPSS software (version 2.2, IBM, Chicago, IL, USA). Quantitative variables were presented as the mean (± SD) and range. Categorical variables were presented as absolute percentages. Descriptive statistics were used to summarize the data. The Mann - Whitney U test was applied to test for statistical significance between both groups. P values < 0.05 were considered significant. Due to the retrospective design of the study, no ethics approval was needed.

RESULTS

Twenty-two patients fulfilled the inclusion criteria for SIPGS. After identification of those patients, the same number of age- and gender-matched LIG patients was recruited by retrospective file review in the same time interval. The diagnosis of gout was confirmed in 19 SIPGS patients and in 21 LIG patients by polarization microscopy. In three SIPGS and in one LIG patient synovial fluid aspiration was not performed due to anticoagulation.

Musculoskeletal ultrasound was performed in all patients. In 21 SIPGS and LIG patients, typical features such as tophi and / or a double contour sign could be detected [10]. Four SIPGS and five LIG patient displayed typical urate depositions in DECT [11]. Fourteen SIPGS and 19 LIG patients had not been diagnosed with gout before. The SIPGS patients had been diagnosed with gout for a mean of 10 years (SD ±10), while only three LIG patients had been diagnosed with gout before, 2, 12 and 36 months before admission, respectively.

All SIPGS and LIG patients were admitted to the inpatient care unit due the severity of gout symptoms.

Patient characteristics at admission of both groups are shown in Table 2**.** The mean visual analogue scale (VAS) for pain, fatigue and general health differed significantly ($p<0.05$) between the two groups. Mean hemoglobin and mean number of thrombocytes diverged significantly ($p<0.05$). Anemia was present in all SIPGS patients, while only observed in 12 LIG patients. The mean number of joints involved was highly significant ($p<0,001$). Interestingly, there was nearly no difference in ferritin levels between the groups. Procalcitonin (PCT), as a marker for bacterial and fungal infections, was determined in 11 SIPGS patients and in four LIG patients and was negative in all patients. Leukocytosis was present in about one third (6 vs. 8 patients), thrombocytosis in 7 vs. 4 patients with SIPGS and LIG, respectively. None of the LIG and three of the SIPGS patients displayed fever.

Ten SIPGS and five LIG patients had a glomerular filtration rate (GFR) of 30-60 ml/min, in two SIPGS and four LIG patients GFR was < 30 ml/min at admission. In eight SIPGS and one LIG patient acute renal failure was observed, defined as >50% increase of creatinine within 48 hours. In four of the eight SIPGS and one LIG patient chronic renal insufficiency had been documented before. In the four SIPGS patients where acute renal failure occurred without previously prevalent chronic renal insufficiency, renal function returned to normal under anti-inflammatory treatment.

Table 2: Patient characteristics at admission.

Characteristics and laboratory parameters	Systemic inflammatory polyarticular gout (mean ± standard deviation)	Low-grade inflammatory gout (mean ± standard deviation)	Significance
Sex [male/female]	18/4	18/4	
Height [cm]	173 ± 7	174 ± 9	0.502
Weight [kg]	85.5 ± 16.5	90.4 ± 13.0	0.074
Body mass index [kg/m^2]	29.0 ± 6.4	29.8 ± 4.2	0.168
Age [years]	67.5 ± 11.3	66.5 ± 12.7	0.888
Visual analogue scale disease activity (0-10cm)	8.0 ± 1.2	6.3 ± 3.5	0.117
Visual analogue scale pain (0-10cm)	8.3 ± 1.1	5.6 ± 3.6	0.005**
Visual analogue scale fatigue (0-10cm)	6.7 ± 2.2	4.6 ± 3.3	0.033*
Visual analogue scale general health (0-10cm)	8.0 ± 1.2	5.1 ± 3.5	0.004**
ESR [mm/h]	91 ± 24	50 ± 27	< 0.001**
CRP [mg/l]	172 ± 84	25 ± 21	< 0.001**
Uric acid µmol/l / mg/dL	491 ± 146 / 8.9 ± 2.65	499 ± 149 / 8,39 ± 2,46	0.935
Hemoglobin[mmol/l]	7.2 ± 0.9	8.4 ± 1.1	0.035*
Leukocytes [G/l]	11.2 ± 3.5	12.7 ± 6.4	0.637
Thrombocytes [G/l]	357 ± 137	288 ± 99	0.08
Neutrophile granulocytes [Gpt/l]	8.2 ± 3.1	7.4 ± 3.0	0.481
Ferritin [µg/l]	391 ± 313	349 ± 306	0.358
Mean joints involved	9.6 ± 3.8	3.7 ± 2.0	< 0.001**
Fever (>38,5°C)	3	0	n.a.
Renal failure	8	1	n.a.

*significant **highly significant

Table 3: Involvement of joint regions in percent.

Disease	Systemic inflammatory polyarticular gout		Low-grade inflammatory gout	
Joint region	Unilateral involvement in number(percentage)	Bilateral involvement in number(percentage)	Unilateral involvement in number(percentage)	Bilateral involvement in number(percentage)
Elbow	4 (18%)	9 (41%)	9 (41%)	0
Wrist	2 (9%)	13 (59%)	5 (23%)	0
Finger joints	3 (14%)	11 (50%)	9 (41%)	0
Knee	4 (18%)	17 (77%)	12 (55%)	0
Ankle	5 (23%)	17 (77%)	3 (14%)	0
MTP 1 joint	4 (18%)	18 (81%)	17 (77%)	11 (50%)
Other MTP joints	3 (14%)	8 (36%)	2 (9%)	0

The details of the joint involvement in both groups are shown in Table 3. In LIG the only joint being affected bilaterally was the MTP I joint in 11 patients, while unilateral involvement was most commonly observed in the MTP I (n=17) and knee joints (n=12). Concerning the SIPGS group, bilateral affection was seen in every patient. Bilateral involvement of MTP I (n=18), ankle (n=17) and knee joints (n=17) were most frequently observed.

The clinical course, imaging results and treatment administered is displayed in Table 4. The SIPGS patients had to be treated 4.5 days longer (median 14 vs. 9.5 days, p=0.017) in the inpatient ward than the LIG patients; while time to admission (median 20 vs. 11 days, p =0.612) was almost twice as long in LIG patients, although this was not found to be significant. Prior general gout symptoms were reported by SIPGS patients for 89 months, by LIG patients for 15 months (p=0,002) before the inpatient admission due to the acute attack.

Concerning the acute treatment, NSAIDs were ineffective and discontinued in all SIPGS patients, while this was only the case in 5 LIG patients, excluding patients in whom NSAIDs were contraindicated due impaired renal function. In SIPGS, more patients received GCs and in two patients Il-1 blockade with canakinumab was administered.

Detailed information about the decrease of CRP during the clinical course is displayed in Table 5. It seemed that decrease

Table 4: Patient course, imaging and treatment.

Disease	Systemic inflammatory polyarticular gout	Low-grade inflammatory gout	Significance
Interval between symptom onset and admission in days (median)	11 (minimal/maximal, 1-30)	20 (minimal/maximal, 0-90)	0,612
Inpatient treatment in days (median)	14 (minimal/maximal, 9-21)	9,5 (minimal/maximal, 7-18)	0,017*
General symptoms of gout in months (median)	89 (minimal/maximal, 0-336)	15 (minimal/maximal, 0-60)	0,002*
Podagra	16 (73%)	18 (81%)	0,477
Tophi (x-ray, ultrasound, DECT)	16 (73%)	13 (59.1 %)	0,346
NSAIDs	6 (27.3%)	5 (22.7%)	0,731
Glukocorticoids	16 (72.7%)	13 (59.1%)	0,346
Colchicin	20 (90.9%)	18 (82%)	0,385
Il-1 inhibitor	2 (9.1%)	0 (0%)	0,152

*significant

Table 5: CRP response from onset and from admission in days..

Disease	Systemic inflammatory polyarticular gout		Low-grade inflammatory gout	
	Time from admission (median)	N	Time from admission (median)	N
CRP < 5 mg/l	9 days	8	9 days	8
CRP < 10 mg/l	8 days	10	11 days	11
CRP < 20 mg/l	6 days	18	7 days	13

N= number of patients

of CRP, although initially higher in the SIPGS group, was almost similar. None of the SIPGS patients were free of symptoms on discharge from hospital and in remission, according to recently published criteria [12], while all LIG patients showed a very good resolution of symptoms and remission.

DISCUSSION

Our study aimed at describing the clinical syndrome of systemic inflammatory polyarticular gout. Although this syndrome obviously occurs more commonly than perceived in clinical practice, no case series has yet been published; and this syndrome remains being not clearly defined. Only three case reports are available in English language(6-8) and one case report in Japanese [13]. These case reports share the following clinical criteria: an acute flare of chronic, poorly controlled, tophaceous, polyarticular gout with fever and markedly raised inflammatory markers (CRP and ESR) in middle to old age male patient. Recently a case series of difficult to treat polyarticular inflammatory gout patients was published [14].

All of our 22 SIPGS patients were admitted to an inpatient care unit due to the severity of their symptoms, which was also reflected by the high VAS scores for disease activity, pain, fatigue and general health. Our SIPGS cohort had a median age of 67 years with a clear male predominance. Overweight (median BMI, 29) was common. The correlation between obesity and hyperuricemia is well known [15,16]. Of note, more than half of the SIPGS patients were newly diagnosed with gout, as well as new to our institution. General symptoms of gout were present with a median of 89 months. This means that previous gout symptoms were either unspecific or not severe enough for patients to consult a physician or for establishing the diagnosis of gout. The median duration of 11 days until clinical admission probably displays that referring physicians were unable to deal with the severe clinical situation adequately in an outpatient setting which is also underlined by the fact that a mean of 10 joint regions were involved. Lawry et al. [17], described 106 consecutive gout patients in a prospective study and found out that 42 (40%) had articular inflammation at two or more sites. Nicholls et al. [8], and Mirsoyev et al. [7], state in their case reports, those patients with a flare of polyarticular gout can exhibit a systemic inflammatory response syndrome that may be misdiagnosed as sepsis. Shah et al. [6], aimed at distinguishing gout from sepsis in their case report. They concluded that clinical examination and imaging findings were unreliable and that microscopic examination of exudates or synovial fluid with both polarized light microscopy and gram stain is necessary for distinguishing inflammatory gout syndrome from sepsis and that early recognition may prompt a trial of GC.

In 16 (73%) of our SIPGS patients, palpable tophi were present. Since only chronic gout leads to the formation of tophi [18], our cohort obviously consisted of patients with longstanding chronic hyperuricemia. This is no surprise, as chronic gout over years causes more severe deposition of uric acid in a higher number of joints. Low-grade fever was only observed in 3 patients (14%). This fact was certainly surprising. It does not support the proposed theory of a systemic inflammatory response syndrome, which was previously described and mentioned with fever [6,8,18]. This may be a parameter to distinguish between gouty arthritis and infectious arthritis. Although the inflammatory markers, CRP and ESR were highly elevated, procalcitonin, which

is specific for bacterial and fungal infection [19] was normal in all 11 SIPGS patients in whom it was determined. Liu et al. [20], described in a Chinese Han population, that PCT correlates with CRP and ESR in patients with a flare of gout. It is unclear why we could not observe this. Possible reasons are, that we had a different laboratory test (Thermo Scientific B.R.A.H.M.S KRYPTOR Random Access Analyser, TRACE™ Technology vs ECLIA, Roche, Cobas6000), in our immunoassay the limit of quantitation was 0.06 ng/ml, this information is not given for the above mentioned publication. Another reason could be the different ethnical patient cohort.

Uric acid levels were high (mean, 491 µmol/l) although these were obtained during the acute gout flare. It may be hypothesized that the levels are much higher when being examined during a time period without systemic inflammation. It has been reported that about 40% of patients presenting with acute gout flares have normal uric acid levels [21,22].

Eight SIPGS patients (36%) had acute renal failure during the polyarticular gout flare. This has not previously described in the literature. In 4 patients renal failure occurred without preexisting chronic renal insufficiency. Elevated uric acid is strongly associated with the development of chronic kidney disease [23]. It is suggested that high uric acid levels could induce oxidative stress and endothelial dysfunction, resulting in the development of both systemic and glomerular hypertension in association with elevated renal vascular resistance and reduced renal blood flow [24-26]. Furthermore, patients might have had dehydration due the inflammatory syndrome. This could explain the normalization of renal function in four of the eight patients, without previous chronic renal insufficiency, after the inflammatory gout flare had resolved.

Treatment of SIPGS with NSAID appears to be insufficient in all patients. It was either contraindicated, or patients had to be switched to alternative drugs because of lack of efficacy. Colchicine and GCs were applied more commonly. Since in two patients the inflammation could not be controlled even with GC, the IL-1β antagonist canakinumab was administered. So et al. [27], described in their single-blind study that canakinumab provides rapid and sustained pain relief in patients with acute gouty arthritis. Furthermore, it significantly reduces the risk of flares compared to GC. Recent randomized clinical trials compared the use of canakinumab with intramuscular triamcinolone acetonide for treatment of acute gout flares [27,28] and concluded that it is superior to the application of intramuscular GC. No controlled trials have compared canakinumab with common first-line therapeutic options, such as NSAIDs or colchicine [29]. In our two patients with refractory SIPGS canakinumab was highly effective.

In most SIPGS patients the inflammatory markers decreased slowly and none of the SIPGS patients was free of symptoms at discharge from hospital, which was observed in all LIG patients. This fact points out that SIPGS is a severe syndrome requiring ongoing intense treatment.

In order to identify our newly defined SIPGS patients better, we included an age-and gender matched LIG group. These patients have also been severely ill as they had been admitted to inpatient care unit. In LIG patients the visual analogue scale for pain, fatigue and general health was significantly ($p<0.05$) lower, which can be easily explained by the lower degree of inflammation. Interestingly the mean hemoglobin and number of thrombocytes differed as well and reached significance ($p<0.05$), which certainly underlines that the SIPGS patients had suffered for a longer time from inflammatory gout, as increase of thrombocytes count and development of anemia are known laboratory signs of inflammation. The inflammatory markers CRP and ESR differed significantly, as well as the mean number of joints involved, which is of course partly explained by the applied inclusion criteria. No LIG patient suffered from fever, in only 1 patient acute-on-chronic renal failure was observed. The only joint being affected bilaterally in 11 LIG patients was the MTP I joint, while all SIPGS patients had a bilateral joint involvement. The MTP 1, ankle and knee joints were the most commonly bilaterally affected joints.

In LIG NSAIDs were discontinued only in 6 patients, while this was the case in every SIPGS patient, displaying that inflammatory activity in SIGPS was so high, that NSAIDs were ineffective or contraindicated. The above mentioned facts surely help in differentiation between these two forms of gout.

Limitations of this study include its retrospective, monocentric design. Further studies are needed in order to better describe the clinical features and treatment outcomes of SIPGS in a larger number of patients.

CONCLUSION

We conclude that patients with SIPGS suffer years before gout symptoms, are severely affected and rarely exhibit fever. Anemia is commonly observed, while leukocytosis and thrombocytosis are rare. Procalcitonin was in our cohort normal, and may help to differentiate this syndrome from sepsis, especially in the case of coexistent fever. Acute renal failure occurs in more than 1/3 of patients. If renal failure does not occur on the basis of chronic renal insuffiency, renal function returns to normal with treatment. NSAID are either contraindicated or ineffective and have to be combined with or replaced by colchicine and GC. In severe cases with inadequate response to standard treatment regimens or refractory inflammatory activity, patients may be treated with IL-1β antagonists. Although inflammatory response can be controlled by conventional therapy in most cases, complete remission is rarely achieved during the rather long inpatient treatment course.

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