

Concomitant Septic Arthritis in Crystal Monoarthritis

LITO ELECTRA PAPANICOLAS, PAUL HAKENDORF, and DAVID LLEWELLYN GORDON

ABSTRACT. Objective. In acute monoarthritis, the presence of crystals in synovial fluid may lead to a diagnosis of crystal arthritis (CA) before septic arthritis (SA) can be excluded by culture. We aimed to identify the frequency of coexistence of CA with SA and to compare these with regard to synovial fluid microscopy, C-reactive protein (CRP), and blood culture.

Methods. We examined 1612 synovial aspirates from 2004 to 2009 retrospectively. Of these, 104 patients with clinically significant SA were identified. These were compared to 295 patients with isolated CA.

Results. Five percent of joints with CA had concomitant infection. A high synovial white blood cell (WBC) count and elevated CRP (> 100 mg/l) were predictive of concomitant SA with a sensitivity of 86.4%, specificity of 48.3% and 54.6%, and negative predictive values of 98.5% and 98.7%, respectively. In patients with SA who had a blood culture, 42.5% were positive with a matching organism. SA of the shoulder had a 90% rate of bacteremia.

Conclusion. Crystals alone in synovial fluid from acute monoarthritis cannot exclude SA, as CA and SA frequently coexist. High WBC counts and elevated CRP are common to both SA and CA. Blood cultures should be collected and septic arthritis considered, even when crystals are present, particularly if the shoulder is affected. The exception is when Gram stain is negative and the CRP is < 100 mg/l and joint WBC count is $< 10,000/\mu\text{l}$. In these circumstances it is very unlikely that there will be concomitant SA. (J Rheumatol First Release Dec 1 2011; doi:10.3899/jrheum.110368)

Key Indexing Terms:

INFECTIOUS ARTHRITIS
C-REACTIVE PROTEIN

GOUT

CALCIUM PYROPHOSPHATE
BACTEREMIA

Monoarthritis due to bacterial infection has significant morbidity and a mortality of 11%^{1,2}. Crystal arthritis (CA) is another common cause of monoarthritis that may be clinically indistinguishable from septic arthritis (SA)³. The finding of crystals on synovial fluid microscopy may lead to a presumptive diagnosis of CA and treatment with corticosteroids rather than antibiotics. However, SA and CA can coexist, leading to misdiagnosis and inappropriate treatment.

Microscopy and culture of synovial fluid represents the “gold standard” for investigation of monoarthritis. Unlike culture, synovial white blood cell (WBC) count, Gram stain, and peripheral blood tests such as C-reactive protein (CRP) can be available quickly to guide initial clinical management. There is a need to establish how useful these tests are in excluding SA compared to the gold standard of synovial fluid culture.

From the Department of Microbiology and Infectious Diseases, SA Pathology, Flinders Medical Centre; and the Clinical Epidemiology and Health Outcomes Unit, Flinders Medical Centre, Adelaide, South Australia.

L.E. Papanicolas, BMBS, Department of Microbiology and Infectious Diseases, SA Pathology; P. Hakendorf, MPH, Clinical Epidemiology and Health Outcomes Unit; D.L. Gordon, FRACP, PhD, Department of Microbiology and Infectious Diseases, SA Pathology.

Address correspondence to Dr. L. Papanicolas, Microbiology and Infectious Diseases, Flinders Medical Centre, Bedford Park, South Australia 5042. E-mail: litop76@gmail.com

Accepted for publication September 15, 2011.

Previous studies identified raised synovial fluid WBC count as correlated with SA, with sensitivity of 50%–64% and specificity of 88%^{4,5} or a likelihood ratio of 2.9 for counts $> 25,000/\mu\text{l}$ ⁶. Laboratory tests such as erythrocyte sedimentation rate, CRP, and peripheral WBC count have high sensitivity but poor specificity⁵. CA itself can cause elevated blood and joint WBC count and inflammatory markers, further reducing the diagnostic utility of these tests.

In the only recent study examining rates of concomitant infection in crystal arthropathy, 4 of 265 (1.5%) cases had concomitant SA⁷. The mean synovial fluid WBC count for CA samples was $23,000/\mu\text{l}$ with WBC counts $> 50,000/\mu\text{l}$ in the 4 septic joints. However, numbers were too small to make meaningful statistical conclusions.

The primary aim of our study was to identify the frequency of coexistence of SA with CA, and to compare these conditions with regard to joint fluid microscopy and CRP. The secondary aim was to document the type of organisms causing SA in our cohort and rates of bacteremia coexisting with SA.

MATERIALS AND METHODS

This was a retrospective study conducted at Flinders Medical Centre, a tertiary care referral facility in a suburban setting. The microbiology laboratory database was queried for all synovial fluid aspirates between January 2004 and April 2009. This identified patients who had an aspirate that either

was culture-positive or had crystals (or both). Further data about these patients were then collected using a second clinical database. Because many patients had multiple episodes of SA or CA during the study period, only 1 sample per patient was included.

Further data collected included age, sex, type of joint aspirated, Gram stain, synovial WBC count, culture result, type of crystal, CRP, and blood culture results within 7 days of joint aspiration. Samples were included in the study if there was growth of a clinically significant pathogen or crystals were seen on fluid microscopy as long as the cell count, site of aspiration, and type of fluid could be verified in the clinical database. In our laboratory it is standard procedure for the microbiologist to discuss all positive culture results from sterile sites with the consulting infectious diseases physician. This physician then reviews the case during the acute admission and determines the significance of the microbiology prior to the finalization of the results. If there was a comment on the report that the organism grown was a probable contaminant, then that sample was excluded from the study.

If the specimen was grossly purulent, grossly blood-stained, or clotted, the joint WBC count was represented semiquantitatively. The result was reported as “+” if there was 1 cell per high powered field on the 100× objective lens, “++” for 2–10 cells, and “+++” for > 10 cells. In this study “+++” was estimated to be at least 10,000 cells/μl, although the actual number was often much higher. Therefore, the results were reported as either greater than or less than 10,000 cells/μl and no mean synovial WBC count was calculated.

All data were analyzed using Stata MP 11.1 software (StataCorp, College Station, TX, USA). Binary data were compared using the chi-square test and Fisher’s exact test was used when numbers were small. Continuous data were examined by t test and/or Wilcoxon rank-sum test. P values < 0.05 were considered significant.

RESULTS

There were 1681 aspirates from 1213 individual patients on the database. Of these, 204 culture-positive aspirates in 185 patients were initially identified. Fifty-three patients’ aspirates were excluded, based on the growth of a probable contaminant. A further 28 patients were excluded for the following reasons: age < 16 years, patient not on clinical database, joint type not indicated, not synovial fluid, or aspirate not from a sterile site. After exclusion, 104 patients (8.6% of all patients) were identified with a culture-positive and clinically significant episode of SA.

There were 600 aspirates from 457 individual patients with fluids positive for crystals on the microbiology database, or 38% of all patients. The crystal types included 325 monosodium urate, 261 calcium pyrophosphate, and 14 aspirates with both types of crystals (Table 1). These data

Table 1. Types of crystals and coexistence of septic arthritis.

Type of Crystal	Total No. Aspirates (percentage of total)	No. Aspirates with Concomitant Septic Arthritis (percentage of total)
Sodium urate	325 (52.9)	13 (4.0)
Calcium pyrophosphate	261 (42.5)	19 (7.3)
Mixed calcium pyrophosphate and sodium urate	14 (2.3)	0
All crystals	600	31 (5.2)

were used to represent the total number of crystal-positive cases during the study period. However, 162 patients’ samples were excluded from further analysis for the following reasons: patient not on clinical database, joint type not indicated, not synovial fluid, positive blood culture, positive synovial fluid culture, or WBC count not recorded. This left a total of 295 patients included in the crystal group.

Concomitant CA and SA were present in 31 aspirates from 22 patients. This constitutes 21% of patients with confirmed SA and 4.8% of total patients (5% of aspirates) with CA before exclusion (Table 1). Concomitant SA was present in 19 (7.3%) of 261 aspirates with calcium pyrophosphate crystals compared to 13 (4%) of 325 aspirates with monosodium urate crystals ($p = 0.10$).

The 104 subjects with clinically significant SA were compared with the 295 cases of CA. The CA group had 159 patient aspirates with monosodium urate crystals, 133 calcium pyrophosphate crystals, and 3 with both types present. Further analysis was performed to assess predictive criteria for the presence of SA, as follows. The demographic characteristics of the groups were similar and are shown in Table 2.

White cell count. The synovial WBC count was recorded semiquantitatively in 87/104 (84%) of septic samples compared to 159/295 (54%) of samples with crystals only. The finding of high synovial WBC count (> 10,000/μl or +++) was common in all groups (Table 3), but significantly more likely to occur in septic joints ($p < 0.001$). All groups had cases with low WBC counts (< 10,000/μl or < +++) including 3 of 22 in the mixed CA/SA group, but this was more likely in the CA group ($p < 0.001$). When compared to cases of CA alone, a high synovial WBC count was predictive of concomitant SA with a sensitivity of 86.4% (95% CI 65.1%–97.1%), specificity of 48.3% (95% CI 42.5%–54.2%), positive predictive value (PPV) of 8.0%, and negative predictive value (NPV) of 98.5% (95% CI 95.9%–99.5%).

C-reactive protein. The mean CRP for patients with SA, patients with CA, and those with mixed CA/SA was 185, 107, and 224 mg/l, respectively (Table 3). The difference between the SA group and the CA group was significant (mean difference 78 mg/l, 95% CI 52.8%–103.1%; $p < 0.001$). Compared to cases of CA alone, a CRP ≥ 100 mg/l was predictive of concomitant SA with a sensitivity of 86.4% (95% CI 65.1%–97.1%), specificity of 54.6% (95%

Table 2. Characteristics of study subjects.

Characteristic	Type of Arthritis		
	Septic Only	Crystal Only	Mixed Septic and Crystal
Number	82	295	22
Mean age, yrs	62	72	76
Male:female	3.3	2.8	3.4

Table 3. Comparison of microscopy, CRP, Gram stain, and blood culture results by type of arthritis.

Type of Arthritis	WBC > 10,000/ μ l	Mean CRP, mg/l	Gram Stain Positive (%)	Positive Blood Culture* (%)
Septic only, n = 82	66 (80)	185 (n = 79)	49 (60)	24 (42)
Crystal only, n = 295	151 (49)	107 (n = 238)	0	0
Calcium pyrophosphate crystal only, n = 133	61 (46)	108 (n = 98)	0	0
Sodium urate crystal only, n = 159	89 (56)	105 (n = 140)	0	0
Mixed septic and crystal, n = 22	19 (86)	224 (n = 22)	12 (55)	7 (44)

* Performed in 57 septic-only cases and in 16 mixed septic and crystal cases. CRP: C-reactive protein; WBC: white blood cells.

CI 48.1%–61.1%), PPV 9.1%, and NPV 98.7% (95% CI 96.4%–99.5%). In the mixed SA/CA group, CRP was < 100 mg/l in 3 of 22 cases, but these were different from the cases that had low synovial fluid WBC count.

Gram stain. Gram stain was positive in 58.7% of all samples that were eventually culture-positive. In the mixed CA/SA group Gram stain was positive in 12 (54.5%) of 22 patients. In all cases the Gram stain organism corresponded to the organism grown subsequently in culture. There were 4 (0.2%) of 1681 samples in which Gram stain was thought after clinical and laboratory review to be a false-positive. Thus Gram stain of synovial fluid had a sensitivity of 58.6% (95% CI 48.6%–68.2%), specificity of 99.7% (95% CI 99.4%–99.9%), PPV 93.8% (95% CI 85%–98.3%), and NPV 97.5% (95% CI 96.6%–98.2%) in relation to its correlation with clinically significant SA.

Of the 10 mixed SA/CA cases with a negative Gram stain, none had both serum CRP < 100 mg/l and synovial WBC count < 10,000/ μ l. Of the 238 crystal samples for which both CRP and WBC counts were recorded, 61 (26%) fell into this category. Of the SA cases without crystals present, 4 (5%) had CRP < 100 mg/l and synovial WBC counts < 10,000/ μ l as well as a negative Gram stain.

Microbiology. Gram-positive organisms predominated, constituting 86% of all organisms cultured. The most common organism cultured from septic joints was *Staphylococcus aureus*, accounting for 60% of all clinically significant organisms cultured. Methicillin-resistant *S. aureus* (MRSA) accounted for 5 cases, 7.9% of *S. aureus* cases, and only 4.7% of the total. Fewer Gram-negative organisms were cultured, with *Pseudomonas aeruginosa* the most common (4.7% of the total). There was only 1 case of gonococcal arthritis (Figure 1).

Blood cultures were performed in 73 patients (70.2%) with confirmed SA, and were positive with the same organism as cultured in synovial fluid in 42.5%. When analyzed by joint type, 9 of 10 patients with shoulder SA had bacteremia (Table 4). Patients with shoulder SA were significantly more likely to have bacteremia than other joint types (risk difference 55.1%, 95% CI 33.1%–77.1%; $p = 0.001$). All cases of shoulder SA were due to staphylococcal infec-

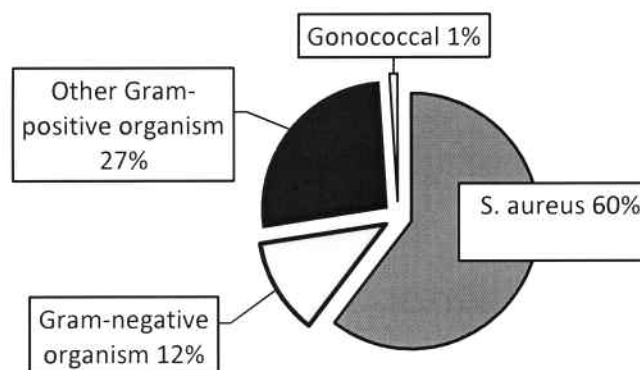


Figure 1. Data represent the microbiology results of 107 organisms cultured from 104 septic joints. Gram-positive organisms 86.9%: *Staphylococcus aureus* 59.8%, other Gram-positive organisms 26.2%; non-gonococcal Gram-negative organisms 12.1%; *Neisseria gonorrhoeae* 1%.

Table 4. Bacteremia rates by joint involved in septic arthritis.

Joint Type	No. with Septic Arthritis	Blood Culture Taken (%)	Blood Culture Positive (%)
Knee	71	42 (59)	16 (38)
Shoulder*	10	10 (100)	9 (90)
Hip	8	7 (88)	2 (29)
Ankle	3	3 (100)	1 (33)
Other	12	11 (92)	3 (27)
Prosthetic	35	20 (57)	10 (50)
Total	104	73 (70)	31 (43)

* Patients with shoulder septic arthritis were significantly more likely to have bacteremia compared to other joint types ($p < 0.05$).

tion. Patients with prosthetic knee joints were more likely to have bacteremia than those with native knee joint infection ($p = 0.086$).

DISCUSSION

Our results show that as a percentage of all joint aspirates with crystals there was concomitant SA in 5.2%. This is considerably higher than the previously published incidence of 1.5% in an American study of 267 joint aspirates⁷. Among samples with confirmed SA, the coexistence of crystals on microscopy

is relatively common, at 21% (22 of 104 patients). In the 10 patients with mixed CA/SA who had crystals but no organisms on Gram stain, it is probable that the patients were treated initially for CA rather than SA. We therefore examined the use of other rapidly available laboratory tests for predicting the presence of coexisting CA and SA.

Gram stain is a rapid test with a high specificity and positive predictive value. It is the most useful test to perform, identifying 59% of cases of SA in this series, similar to previously published data^{2,6}. If positive, the joint must be treated as septic, but Gram stain does not have adequate sensitivity to exclude SA. There is more difficulty in clinical decision-making when the synovial fluid Gram stain is negative. In many cases both plasma CRP and synovial WBC count will also be elevated and in these cases concomitant SA cannot be excluded. However, lower plasma CRP (< 100 mg/l) and lower synovial WBC (< 10,000/ μ l) each have high negative predictive values. When found together, SA is unlikely to be present.

Systemic sepsis with a matching organism was found in 42% of the SA group. The rates of positive blood culture and the microbiological profile are similar to previously published data^{1,2,3,8}. Interestingly, there was a very high rate of bacteremia associated with shoulder arthritis in our series (9/10 cases), with all cases due to staphylococcal infection. This is a higher incidence of bacteremia in shoulder arthritis than previously reported⁹. Previous reviews of SA of the shoulder have shown it to be more resistant to treatment and more frequently associated with older age and comorbid conditions^{9,10,11}. Bacteremia may also be more common because of more subtle presentations and later diagnosis. The implication of this is that when acute shoulder arthritis in a febrile patient is observed, blood cultures and prompt systemic antistaphylococcal treatment should be initiated as there is likely to be systemic, not just local, infection.

Limitations to this study include the following: data were collected retrospectively; clinical significance was based on recording by the microbiologist's entry on the computer database rather than clinical case note review. Also, the numbers of concomitant SA with negative Gram stain were small (10) and the findings need to be taken in this context. Many synovial WBC counts were reported semiquantitatively and this type of reporting was much more likely to occur in the septic specimens. This reflects the much higher likelihood of these specimens being grossly purulent and

therefore unsuitable for precise cell counts. Although the inclusion of semiquantitative data for joint WBC counts may be seen as a limitation, we decided to include these data in our analysis because often this is the only type of result available to clinicians.

The presence of crystals alone in synovial fluid in patients presenting with acute monoarthritis cannot exclude infection, because septic arthritis and crystal arthritis frequently coexist. High synovial fluid WBC counts and elevated CRP are common to both conditions and cannot reliably distinguish the two. Bacteremia in septic arthritis, especially of the shoulder, is common. Blood cultures should be collected and empirical antibiotic therapy considered in most cases of monoarthritis even if crystals are detected. The exception is in cases where there is a negative Gram stain with both plasma CRP < 100 mg/l and joint WBC count < 10,000/ μ l. In these circumstances it is unlikely that there will be concomitant septic arthritis.

REFERENCES

1. Gupta MN, Sturrock RD, Field M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. *Rheumatology* 2001; 40:24-30.
2. Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and outcome of septic arthritis in a single UK Health District, 1982-1991. *Ann Rheum Dis* 1999;58:214-19.
3. Baker DG, Schumacher HR Jr. Acute monoarthritis. *N Engl J Med* 1993;329:1013-20.
4. Li SF, Henderson J, Dickman E, Darzynkiewicz R. Laboratory tests in adults with monoarticular arthritis: Can they rule out a septic joint? *Acad Emerg Med* 2004;11:276-80.
5. Li SF, Cassidy C, Chang C, Gharib S, Torres J. Diagnostic utility of laboratory tests in septic arthritis. *Emerg Med J* 2007;24:75-7.
6. Margaretten ME, Kohlwes J, Moore D, Bent S. Does this adult patient have septic arthritis? *JAMA* 2007;297:1478-88.
7. Shah K, Spear J, Nathanson LA, McCauley J. Does the presence of crystal arthritis rule out septic arthritis? *J Emerg Med* 2007; 32:23-6.
8. Yu KH, Luo SF, Liou LB, Wu YJ, Tsai WP, Chen JY, et al. Concomitant septic and gouty arthritis — an analysis of 30 patients. *Rheumatology* 2003;42:1062-6.
9. Lossos IS, Yossepowitch O, Kandel L, Yardeni D, Arber N. Septic arthritis of the glenohumeral joint. A report of 11 cases and review of the literature. *Medicine* 1998;77:177-87.
10. Leslie BM, Harris JM, Driscoll D. Septic arthritis of the shoulder in adults. *J Bone Joint Surg Am* 1989;71:1516-22.
11. Kelly PJ, Coventry MB, Martin WJ. Bacterial arthritis of the shoulder. *Mayo Clin Proc* 1965;40:695-9.