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Original article

Combining cytology and microcrystal detection in nonpurulent joint fluid benefits the diagnosis of septic arthritis

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ABSTRACT

Objective: To evaluate the performance of combined cytology and microcrystal detection in joint fluid for diagnosing septic arthritis.
Methods: Retrospective single-center study of joint fluid samples from patients with manifestations suggesting acute or chronic arthritis. The absolute leukocyte count (/mm^3) was recorded; as well as the differential counts, particularly of neutrophils (%). Microcrystals were sought and bacteriological cultures performed. Septic arthritis was defined as positive cultures of joint fluid or blood samples. Diagnostic performance was assessed based on sensitivity, specificity, the receiver-operating characteristics (ROC) curve with the area under the curve (AUC), and the positive and negative likelihood ratios (LR+ and LR−).
Results: Two hundred and eight joint fluid samples were included. The diagnoses were septic arthritis (n = 28), chondrocalcinosis (n = 41), gout (n = 28), rheumatoid arthritis (n = 33), spondyloarthritis (n = 31), osteoarthritis (n = 18), and undifferentiated arthritis (n = 29). Among cytological parameters, those having the best diagnostic performance were the neutrophil count (cutoff, > 50,000/mm^3), the leukocyte count (cutoff, > 50,000/mm^3), and the percentage of neutrophils (cutoff, > 95%); corresponding LR+ values were 8.93, 5.76, and 4.55, respectively. Neutrophil percentages lower than 80% had an LR− value of 0.07. Combining these cytological variables with the absence of crystals improved the diagnostic performance, yielding LR+ values of 11.36, 10.94, and 10.82 for neutrophils > 95%, neutrophils > 50,000/mm^3, and leukocytes > 50,000/mm^3, respectively.
Conclusion: Combining cytological characteristics of joint fluid with the absence of crystals benefits the diagnosis of septic arthritis.

1. Introduction

Septic arthritis is a diagnostic emergency, as only prompt and effective antibiotic treatment can lessen the high risk of life-threatening sepsis and function-threatening joint destruction [1–3]. Although rare, septic arthritis accounts for 25% of all cases of monoarthritis seen at emergency departments. The annual incidence is about 5.7/100,000 population overall and is increased by joint replacement surgery and rheumatoid arthritis (RA) [4–6]. Despite the importance of rapid antibiotic therapy, samples must be collected first, to ensure identification of the organism. The definite diagnosis of septic arthritis rests on identification of a bacterial or fungal pathogen in a joint fluid specimen. Smears are positive in less than half the cases, often due to a small bacterial inoculum, whereas cultures are positive in about 80% of cases. In about 20% of cases, all microbiological specimens remain negative [7–9]. These false-negative results may be ascribable to the inappropriate administration of antibiotics before sample collection or to the fastidious nature of the causative organism.

Although the diagnosis is urgent, the mean time to diagnosis in patients presenting with arthritis is about 3 days [10]. Obtaining diagnostic orientation before the microbiological results are available is therefore extremely useful. Information can be obtained from the medical history, clinical findings, and results of initial blood and joint fluid tests. Nevertheless, several studies indicate that this information fails to contribute significantly to the diagnosis of septic arthritis in a patient presenting with acute arthritis.

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Microbiological studies of a joint fluid sample are essential to the diagnosis of septic arthritis [3,6,11]. However, useful information can also be obtained from the cytological characteristics of the joint fluid (absolute and differential leukocyte counts) and from tests for microcrystals. A leukocyte count greater than 2000/mm^3 points to inflammation, whereas lower counts suggest a mechanical disorder [12–14]. Features classically taken to indicate septic arthritis include cloudy or turbid joint fluid, a nucleate cell count greater than 50,000/mm^3, or a high percentage of neutrophils [15,16]. Many studies suggest that diagnostic information may also be provided by assaying other joint fluid compounds such as lactic acid, glucose, interleukin-6, and uric acid [17–19]. Nevertheless, these parameters are insufficient, as they may be positive also in other joint diseases such as crystal-induced arthritis and inflammatory joint disease [20,21]. Furthermore, infection developing concomitantly with crystal-induced arthritis may be overlooked when the joint fluid examination shows microcrystals [22,23]. Several studies have sought to improve diagnostic performance by combining joint fluid markers. Although promising results have been reported, some of the markers used are not available in everyday practice [17].

Crystal-induced arthritis is the main differential diagnosis in septic arthritis, as the clinical manifestations may be similarly prominent and the joint fluid findings comparable [21,23,24]. No studies have evaluated the performance of considering both cytological variables and the presence of absence of microcrystals in joint fluid samples for the diagnosis of septic arthritis. The objective of this study was to evaluate the performance of combining cytology and microcrystal detection in nonpurulent joint fluid for the diagnosis of septic arthritis.

2. Methods

This single-center retrospective study included patients older than 18 years enrolled in either of two cohorts established at the rheumatology department of the teaching hospital in Rennes, France. One was the SPECTROSYNO [25] cohort of patients with acute or chronic monoarthritis, oligoarthritis, or polyarthritis investigated by joint aspiration between 2010 and 2014. The other source of patients was the DNAr16S cohort [26] of patients who underwent joint aspiration between May 2006 and June 2008 for onset of monoarthritis or oligoarthritis within the last 6 weeks.

2.1. Joint fluid analysis

We included those patients for whom all the following joint fluid data were available: absolute leukocyte count (/mm^3), differential leukocyte count including the percentage of neutrophils, polarized light microscopy examination for microcrystals, and bacteriological cultures. The absolute leukocyte count and percentage of neutrophils were determined at the bacteriology laboratory using a manual technique of reference with a Kova Glasstic Slide (KOVA International, Garden Grove, CA, USA). Each of the ten counting chambers on the slide can contain 1 mm^3 of joint fluid and is equipped with a counting grid (9 large squares containing 0.1 mm^3 each and divided into 9 small squares containing 0.01 mm^3 each). We excluded patients whose cytological results were expressed semi-quantitatively (e.g., scarce or abundant leukocytes), as well as patients with incomplete joint fluid data.

2.2. Diagnoses in the study patients

The cause of the arthritis was determined by the rheumatologist based on all available data, including clinical findings, blood and joint fluid test results, and the radiographic appearance. Pyogenic septic arthritis was defined as arthritis with the recovery of a pyogenic organism from the joint fluid or blood samples. We excluded patients with septic arthritis due to nonpyogenic organisms (e.g., *Mycobacteria*, *Borrelia*, or fungi) and septic arthritis without microbiological documentation. Crystal-induced arthritis was defined as arthritis manifestations consistent with the presence of calcium pyrophosphate dehydrate (CPPD) crystals or monosodium urate (MSU) crystals in the joint fluid and negative results from cultures of joint fluid and blood samples. The definition of inflammatory joint disease was a history of inflammatory joint disease diagnosed and treated by a rheumatologist, clinical manifestations consistent with a flare of the disease, and absence of both microorganisms and MSU crystals in the joint fluid sample. Patients with inflammatory joint disease were further classified as having RA or spondyloarthritis. Mechanical joint disease was defined as a flare of joint congestion, fewer than 2000 nucleate cells/mm^3 in the joint fluid sample with no crystals, and radiographic evidence of osteoarthritis or epiphyseal avascular necrosis. Finally, undifferentiated arthritis was defined as inflammatory joint fluid (> 2000 nucleate cells/mm^3) with no crystals or microorganisms, negative tests for anti-citrullinated peptide antibodies, and absence of clinical and radiographic findings indicating RA or spondyloarthritis at the time of the study.

2.3. Statistics

The statistical analyses were performed with SPSS Statistics software version 20.0 (IBM, Armonk, NY, USA). A Z-test was used to compare multiple qualitative variables ($k > 2$) and Bonferroni's correction was applied to the P values. Multiple quantitative variables ($k > 2$) were compared using analysis of variance (ANOVA). Diagnostic performance was assessed by computing sensitivity and specificity, plotting the receiver-operating characteristics (ROC) curve and computing the area under the curve (AUC), and determining the positive and negative likelihood ratios (LR+ and LR−, respectively). The post-test probability of septic arthritis was considered strong when LR+ was > 10 or the ROC-AUC was > 0.85. LR- values < 0.10 were taken to indicate a low post-test probability of septic arthritis. P values less than 0.05 were considered significant.

3. Results

3.1. Characteristics of the study population

Of the 258 patients in the two cohorts (198 in SPECTROSYNO and 66 in DNAr16S), 214 (83%) had complete data on joint fluid cytology and microcrystals. Finally, 208 joint fluid samples were included in the study. The diagnoses were as follows:

- septic arthritis, $n = 28$;
- chondrocalcinosis, $n = 41$;
- gout, $n = 28$;
- RA, $n = 33$;
- spondyloarthritis, $n = 31$;
- osteoarthritis, $n = 18$;
- undifferentiated arthritis, $n = 29$ (Fig. 1).

The following bacteria were recovered in the patients with septic arthritis:

- *Staphylococcus*, $n = 18$ (methicillin-susceptible *S. aureus*, $n = 14$ and coagulase-negative *Staphylococcus*, $n = 4$);
- *Streptococcus*, $n = 7$ (25.0%) (*Streptococcus* sp., $n = 6$ and *Enterococcus faecalis*, $n = 1$);
- Gram-negative rod, $n = 1$;