Original Article

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Infectious versus non-infectious causes of oligoarticular inflammatory arthritis: A prospective study from a tertiary care hospital in north India

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Summary **Oligoarticular arthritis (inflammation of upto 4 joints) has a wide range of infectious and non-infectious etiologies. The aim of our study was to identify the features which could help in the differentiation of infectious from non-infectious arthritis. The study was prospective and observational, and included 100 patients with oligoarticular inflammatory arthritis. The final diagnosis was made using standard diagnostic criteria and the patients were categorized into infectious and non-infectious groups. Among the 100 patients who were recruited, the following final diagnosis were made: peripheral spondyloarthritis (*n* = 37), axial spondyloarthritis (*n* = 11), tuberculosis (*n* = 19), brucellosis (*n* = 6), septic arthritis (*n* = 6), gouty arthritis (*n* = 5), early rheumatoid arthritis (*n* = 5), non-tubercular mycobacteria (*n* = 2), SLE (*n* = 2), post-chikungunya arthritis (*n* = 2), acute lymphocytic leukaemia (*n* = 1), pachydermoperiostosis (n = 1), sarcoidosis (n = 1) and juvenile idiopathoic arthritis (*n* = 1). The patients were categorized into two groups: infectious (33) and non-infectious (60). The presence of monoarthritis, clinically-significant weight loss, hepatomegaly, splenomegaly and erosive arthritis were significantly more common in the infectious group as compared to the non-infectious group.**

Keywords: Axial spondyloarthritis, peripheral spondyloarthritis, tuberculosis, brucellosis

1. Introduction

Musculoskeletal pain is among the commonest symptoms with which patients present in outpatient clinics. A fraction of these patients are diagnosed with arthritis. Although polyarthritic diseases like rheumatoid arthritis have been widely studied, the epidemiology of oligoarticular arthritis remains less explored. Oligoarticular arthritis, defined as the involvement of upto 4 joints, is routinely encountered in clinical practice. It has a wide range of infectious (*e.g.*: tuberculosis, brucellosis and septic arthritis) as well as non-infectious (*e.g.*: crystal-induced arthritis, peripheral and axial spondyloarthropathies, early rheumatoid arthritis and sarcoidosis) causes. In the studies from developed countries, non-infective causes have been found to be more common than infectious causes. Although not many studies on the clinical and demographic profile of oligoarthritis in Indian patients are available, it is possible that the clinical profile of Indian patients would be different from those of the developed countries due to the higher prevalence of tuberculosis and other infectious diseases.

The clinical presentations of infectious and non-infectious oligoarthritis overlap significantly, which makes a clinical distinction extremely difficult.

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However, it is important to identify the infectious causes of arthritis early as prompt initiation of antibiotics can reduce the extent of the damage to the joint, thereby reducing future disability and morbidity. Therefore, the purpose of the study was to describe the epidemiology of oligoarticular arthritis and identify the demographical, clinical, laboratorical and radiological findings which could help in the differentiation of infectious from non-infectious arthritis.

2. Materials and Methods

The study was designed as a prospective, observational study and prior approval was obtained from the institutional ethics committee. Subsequently, 100 patients who presented to the outpatient and inpatient services of our hospital between June 2017 and November 2018 with oligoarticular arthritis were recruited into the study. An informed consent was taken from all the patients. Patients with clinically evident osteoarthritis, neuropathic joint disease and those with history of significant prior trauma to the bones or joints were excluded from the study. The history and physical examination findings were recorded using a predefined questionnaire. Routine laboratory investigations were performed in all patients, which included routine haemogram, liver and renal function tests, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Apart from these, appropriate specific immunological and microbiological tests like IgM and IgG Enzyme linked immunosorbent assay (ELISA) for brucellosis, Human Leukocyte Antigen-B27 (HLA B-27), rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), angiotensin-converting enzyme (ACE) levels, urine for Chlamydial polymerase chain reaction assay (PCR), stool culture for *Shigella* spp. and *Salmonella* spp., stool for *C. difficile* toxin ELISA, synovial fluid for Gene Xpert, Ziehl-Neelsen stain and Mycobacterial culture were performed according to the physician's discretion depending on the clinical presentation of the patient. All patients also underwent a chest radiograph as well as one radiographic projection of the affected joints to look for erosions. Depending on the clinical scenario, other radiographs and magnetic resonance imaging (MRI) were performed on a case to case basis. The patients were then assigned a final diagnosis based on the standard, disease-specific criteria. Axial and peripheral spondyloarthritis were diagnosed according to the Assessment of Spondyloarthritis International Society (ASAS) classification criteria (*1,2*). Crystal-induced arthritis was diagnosed based on the presence of compatible clinical presentation and hyperuricemia with or without demonstration of crystals in the synovial fluid aspirate (*3*). Sarcoid arthropathy was diagnosed on the basis of the clinical, radiological and histopathological findings (*4*). Early Rheumatoid arthritis was diagnosed as per the American College of Rheumatology/European League against Rheumatism Criteria (ACR/EULAR, 2010) (*5*). Systemic lupus erythematosus (SLE) was diagnosed according to the ACR classification criteria (*6*). Arthritis from tubercular and non-tubercular mycobacteria as well as septic arthritis was diagnosed based on the clinical and radiological features with or without microbiological confirmation (*7*). Brucella arthritis was diagnosed based on a positive IgM/ IgG ELISA or standard agglutination test. After assignment of the final diagnosis, all the recruited patients were categorized into the two groups of infectious and non-infectious arthritis. These groups were then compared for the distribution of clinical parameters like age, fever, weight loss, lymphadenopathy, skin rash, hepatomegaly and splenomegaly. The radiological findings which were compared included the presence of lung manifestations on the chest radiograph, the number of joints involved, axial skeleton involvement and presence of erosive arthritis. Among the lab parameters, ESR and CRP were compared between the two groups. The patients who could not be categorized unambiguously into either of the two groups were excluded from the analysis.

For statistical analysis, all the data were presented as mean ± standard deviation (SD) or median with interquartile range where appropriate. The analysis was performed using the STATA software, version 11 (StataCorp, TX, USA). Any differences in the distribution of the evaluated attributes between the two groups (infectious and non-infectious) were evaluated using the chi square or Fisher's exact test. A p-value < 0.05 was considered as statistically significant.

3. Results

The study had a total of 100 patients. The age of the study population ranged from 14 to 60 years, the mean age being 30.5 ± 13 years. A male dominance was observed (67% of the patients). The most common age group was 21-30 years (35%, n = 35).

The most common symptoms were fever and weight loss, which were present in 59% and 31% of the patients respectively. The median duration of fever was 30 days (range: 10-120 days). History of cattle exposure and travel to outside of India were present in 17% and 6% respectively. The most common physical examination finding was skin rash (16%), followed by splenomegaly (12%), lymphadenopathy (12%), hepatomegaly (11%), enthesitis (7%), dactylitis (3%) and orchitis (2%). Serology for the human immunodeficiency virus and hepatitis C virus was positive in 5% and 1% of the patients respectively.

A total of 23% of the patients had acute arthritis (duration < 6 weeks) at presentation, whereas 77% had chronic arthritis (duration above 6 weeks). The median duration of arthritis was 110 days (range: 30-660 days). The average number of joints involved was

2.1, with 33 patients having monoarticular involvement and 39, 12, 16 patients having two, three and four joints involvement respectively. Concomitant sacroiliitis was present in 17%, among whom 12 had unilateral involvement and 5 had bilateral disease. Majority of the patients showed only large joint involvement (95%), with 72% having lower limb involvement, 8% having upper limb involvement and the remaining 15% having involvement of both the upper and lower limbs. On the other hand, exclusive small joint involvement was seen only in 1% of the patients. Both large and small joints were involved in 4%. Knee joint was the most commonly affected joint, followed by the ankle, hip, wrist, elbow, shoulder and metacarpophalangeal joints. Axial skeleton involvement (excluding degenerative changes) was seen in 20 patients, whereas erosive arthritis was present in 23 patients (Figure 1).

The final diagnosis of all patients is compiled in Figure 2. Prodromal diarrhea (n = 2) or concomitant urinary tract infection (n = 5) was present in 7 patients who had axial and peripheral spondyloarthritis. Polymerase chain reaction (PCR) assay for *Chlamydia trachomatis* was positive in the urine sample in 3 patients. Among the 19 patients who were diagnosed with tuberculosis, 15 had tubercular arthritis and 4 had osteomyelitis with secondary involvement of the adjacent joint. Tubercular involvement at other sites was seen in 7 patients. The individual patterns of joint involvement in peripheral and axial spondyloarthritis, tubercular arthritis, brucellosis and septic arthritis are summarized in Table 1.

The patients were categorized into two groups: infectious (n = 33) and non-infectious (n = 60) (Table 2). Six patients were excluded from the analysis since these patients had a mixed infective and inflammatory clinical picture and exact cause of the arthritis could not be established. These included cases of peripheral and axial spondyloarthrithis in patients who had concomitant hepatitis-C (HCV) and human retroviral (HIV) infection as well as those who had post-chikungunya arthritis.

When the infectious and non-infectious groups were compared, the presence of weight loss ($p < 0.001$), hepatomegaly ($p = 0.04$), splenomegaly ($p = 0.001$) and erosive arthritis ($p = 0.001$) were significantly more prevalent in the infectious group. Mono-arthritis was also more common in the infectious group ($p < 0.001$).

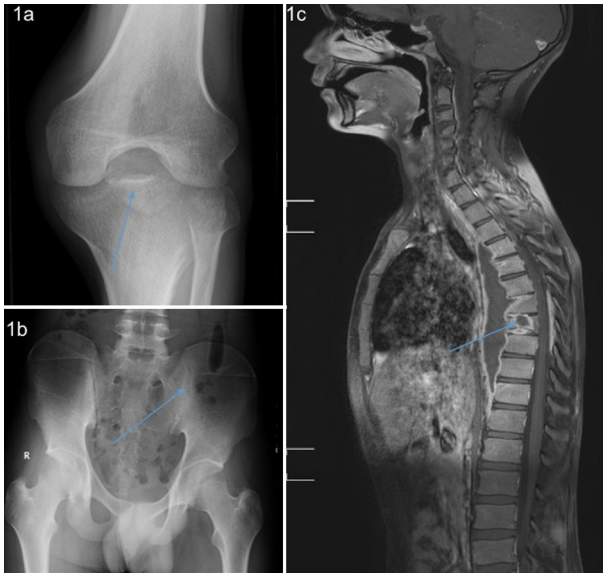

Figure 1. Three patients with different osteoarticular manifestations of tuberculosis. (a) Anteroposterior radiograph of the left knee showing widened intercondylar notch of femur along with small erosion in the tibia (arrow). **(b)** Anteroposterior radiograph of the pelvis showing reduction of the left sacroiliac joint space with sclerosis involving both iliac and sacral sides, suggestive of sacroiliitis. **(c)** Post-contrast T1-weighted sagittal images of the spine showing a large paravertebral collection from D4 toD10 levels along with spondylodiscitis at the D8-D9 level and abscess formation within the D8 vertebra.

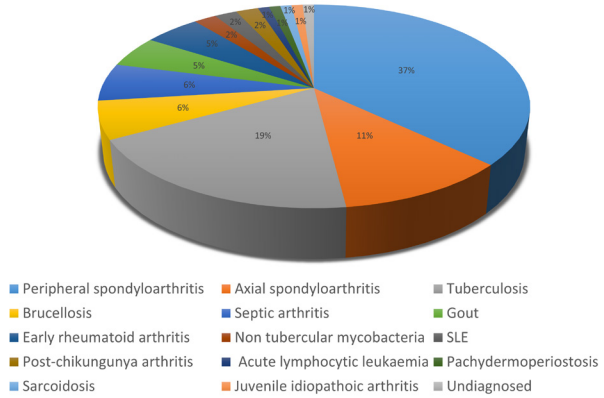

Figure 2. Pie diagram showing the final diagnosis in our patients with oligoarthritis (n = 100).

Table 1. Features of joint involvement in the commonest causes of oligoarthritis in our study

Characteristics	Peripheral spondyloarthritis (37%)	Axial spondyloarthritis (11%)	Tubercular arthritis (19%)	Brucella arthritis (6%)	Septic arthritis (6%)
Number of joints					
1	7	2	14	2	4
> 1	30	9	5	4	2
Most common joint	Knee	Knee	Knee	Knee	Hip
Duration (Acute: Chronic)	13:24	0: 11	2: 17	0: 6	3:3
Axial skeleton involvement	0	11	4	2	2
Erosive arthritis	3	3	10	1	2

Table 2. Comparison of the demographic, clinical, laboratorical and radiological findings in patients with infection and non-infectious causes of oligoarthritis

Characteristics	Infectious (n = 33)	Non-infectious (n = 60)	p-value
Age in years (mean)	29	30.6	0.59
Fever	22 (66.7%)	33 (55%)	0.27
Weight loss	22 (66.7%)	9 (15%)	< 0.001
Lymphadenopathy	7 (21.2%)	5 (8.3%)	0.08
Skin Rash	3 (9.1%)	10 (16.7%)	0.31
Hepatomegaly	7 (21.2%)	4 (6.7%)	0.04
Splenomegaly	8 (24.2%)	4 (6.7%)	0.01
Number of joints			
1	21 (63.6%)	12 (20%)	< 0.001
>1	12 (36.4%)	48 (80%)	
Axial skeleton involvement	7 (21.2%)	11 (18.3%)	0.74
Erosive arthritis	15 (45.4%)	8 (13.3%)	0.01
Erythrocyte sedimentation rate (median)	44	38	0.47
C- reactive protein (median)	59	18.9	0.69

4. Discussion

Axial and peripheral spondyloarthritis was the most common diagnosis in our patients. Similar to previous studies, our study also showed a male dominance in patients with axial and peripheral spondyloarthritis (*8-12*). Lower limb asymmetric oligoarthritis was the most common pattern observed in the above studies, with knee being the commonest joint involved. In one study of axial spondyloarthritis, 65.7% of the patients also had concurrent peripheral joint involvement (*9*). Prodromal diarrhea or urinary tract infection was present in 7 patients with axial and peripheral spondyloarthritis. PCR assay for *Chlamydia trachomatis* was positive in the urine sample in 3 patients. This subset of patients could be classified as reactive arthritis, which usually results from inflammatory response to the microbial invasion of the joints. In a study from India, Chlamydia PCR was positive in the synovial fluid in 23.6% of the patients with reactive arthritis and undifferentiated spondyloarthropathies (*13*). In cases of post-Chlamydial reactive arthritis, treatment with anti-Chlamydial agents have shown no benefits in most studies except for a small randomized trial where prolonged course of combination antibiotics (doxycycline or azithromycin and rifampicin) was associated with better outcome (*14*). We treated all patients who showed urine PCR positivity with anti-inflammatory agents and a single dose of azithromycin.

All the five patients who were diagnosed with gouty arthritis were males and the mean age was 50.6 ± 5.9 years. The most common joint involved was ankle, followed by the metatarsophalangeal joints. Previous studies also have shown a male preponderance with metatarsophalangeal joints, knee and ankle being the most common sites of involvement (*15*). Tubercular arthritis is among the commonest causes of infectious arthritis in endemic areas. It was observed to be the third most common cause of extra-pulmonary tuberculosis in one series (*16*). In a retrospective study of 99 patients who had osteoarticular tuberculosis, arthritis and osteomyelitis was seen in 28% and 10% respectively (*17*). As with many of the previous studies, monoarthritis was the commonest presentation (74%) (*18*). Brucella arthritis was the other major cause of infectious arthritis in our study. Considering the high prevalence of exposure to cattle and unpasteurized milk in the Indian population (17% in our study), this finding is not surprising. Reports of brucellosis have been on a steady rise in India over the past few years. In a review of 792 cases of brucellosis from India, joint involvement was seen in 23.1% (*19*). Hip and knee were the commonest joints involved (*20*). In comparison, in our study, knee was the most common joint involved. Septic arthritis was another important cause of infectious arthritis in our study. Previous studies have shown monoarthritis to be the commonest presentation of septic arthritis, except in 10-20% who may have polyarticular involvement (*21*). 67% of our patients with septic arthritis had monoarthritis. Similar to the previous studies, hip and knee were the commonest joints involved (*21*).

Oligoarthritis from both infectious and non-infectious causes are associated with significant morbidity. However, the infectious arthritis can be treated effectively with anti-microbials. Prompt identification and treatment of infections may prevent further joint damage and reduce future disability and morbidity. Due to similarities in the clinical presentation of infectious and non-infectious causes, it is pertinent to identify the factors which could help in the early identification of infectious arthritis. We found that those patients with clinically-significant weight loss, hepatosplenomegaly, erosive arthritis and monoarthritis were more likely to have an infectious cause for their arthritis than non-infectious causes.

Our study had some limitations. The sample size was too small to draw definite conclusions. However, this study points towards a potential area for future research having significant translational

value and clinical impact. Larger studies would be needed to validate our findings. We also had to exclude patients in whom the cause for the arthritis could not be definitively established as infectious or non-infectious. These included patients with known HIV and HCV infection who were newly diagnosed with spondyloarthropathies since it could not be definitely disproven whether these infections were directly responsible for the joint manifestations or not. Similarly, patients with post-chikungunya arthritis were also excluded as several studies have previously shown that the joint manifestations in chikungunya were secondary to inflammatory response towards the virus from the synovial macrophages.

In conclusion, the presence of clinically-significant weight loss, hepatosplenomegaly, mono-arthritis and erosive arthritis could potentially direct the primary care physician to suspect an infectious cause of arthritis as against a non-infectious cause and start appropriate anti-microbial agents promptly so as to obtain better clinical outcome and limit or prevent future morbidity.

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