SHORT REPORT

Diagnostic value of synovial fluid adenosine deaminase level in tuberculous arthritis

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Abstract

Although body fluid adenosine deaminase (ADA) level is useful for diagnosing tuberculosis but little is known about joint fluid ADA level in tuberculous (TB) arthritis. This study aimed to evaluate the diagnostic value of synovial fluid ADA (SF-ADA) in TB arthritis. Of 43 patients enrolled, nine had confirmed TB arthritis. Fourteen had non-TB septic arthritis, and 20 patients had non-infectious etiologies. The SF-ADA levels were significantly elevated in patients with TB arthritis compared to those with non-infectious origin ($P < 0.05$). All SF-ADA levels were 76 ≥ U/L in TB arthritis and ≤ 60 U/L in non-infectious synovial fluid. The ADA was not different between TB arthritis and non-TB septic arthritis ($P = 0.87$). The possibility of identifying synovial fluid with an ADA under 60-76 U/L of tuberculous etiology may be very low. In addition, an SF-ADA ≥76 U/L with negative ordinary bacterial culture results is highly suspicious for TB arthritis.

Keywords: Tuberculosis, Arthritis, Adenosine Deaminase, Synovial Fluid.

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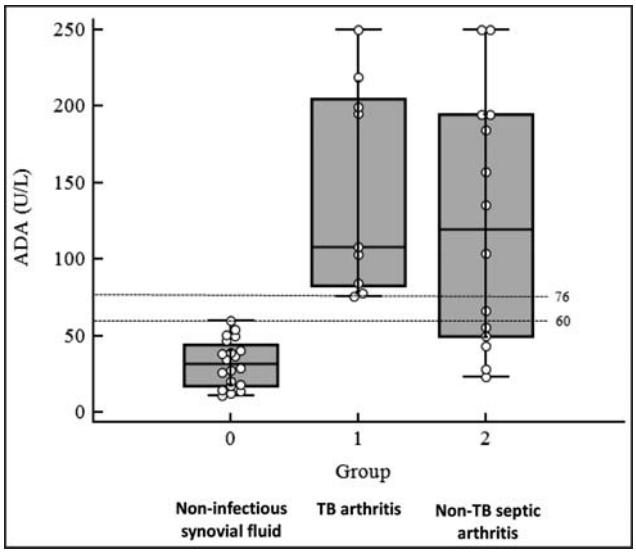
Introduction

Diagnosis of tuberculosis is often difficult when extrapulmonary sites are involved. In particular, tuberculous (TB) arthritis is rare among extrapulmonary tuberculosis cases, and direct acid-fast bacilli (AFB) staining of joint fluid is often negative, with an estimated sensitivity of only 20%.[1] Cultures for Mycobacterium tuberculosis take up to eight weeks before becoming positive. Consequently, extensive joint destruction may develop due to delayed diagnosis. Therefore, a simple and quick biomarker for diagnosing TB arthritis is needed. Body fluid adenosine deaminase (ADA) has good sensitivity and specificity for diagnosing TB pleurisy, TB peritonitis, and TB meningitis.[2-4] However, studies on the diagnostic ability of synovial fluid ADA (SF-ADA) to detect TB arthritis are limited. This report evaluates the diagnostic usefulness of SF-ADA in tuberculosis compared with non-TB joint fluid.

Methods and Results

We performed a retrospective observational study from January 2011 to July 2015. Since South Korea has an intermediate incidence of tuberculosis (66/100,000 population in 2018)[5], ADA measurement is commonly included in routine body fluid analyses. We enrolled patients who had synovial fluid ADA test results, based on a review of their medical records. ADA activity was determined with an ADA-N kit (Denka Seiken Co. Ltd, Japan) and an automated analyser, Toshiba 200FR (Toshiba Co. Ltd, Japan). The institutional board of the Chungnam National University Hospital approved this study, and the requirement for informed consent was waived.

TB arthritis was diagnosed in the presence of any of the following: positive fluid or tissue culture for M.



Note: Horizontal lines in the boxes represent the median values. SF-ADA values from all the TB arthritis patients were ≥ 76U/L, while those of all cases with non-infectious origins were ≤ 60U/L (dash lines). The ADA upper detection limit was 250 U/L according to the manufacturer. ADA, adenosine deaminase; TB, tuberculous.

Figure: Boxplot of synovial fluid ADA (SF-ADA) level according to diagnostic category for all study subjects (n = 43).

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Table-1: Characteristics of the study population. (n=43).

	Tuberculous arthritis, n = 9	Nontuberculous septic arthritis, n = 14	Non-infectious arthritis, n = 20
Age, median year (range)	61 (85-38)	67 (84-33)	54.5 (75-19)
Sex Male	5 (55.6%)	9 (64.3%)	11 (55%)
Female	4 (44.4%)	5 (35.7%)	9 (45%)
Involved joint			
Knee	4 (44.4%)	8 (57.1%)	14 (70%)
Hip	1	2	2
Ankle	0	0	3
Shoulder	2	2	0
Elbow	1	1	1
Wrist	1	1	0
Etiology/	Mycobacterium tuberculosis, 9 (100%)	Staphylococcus aureus, 10 (71%) Staphylococcus epidermidis, 1 Burkholderiacepacia, 1 Klebsiella oxytoca, 1 Candida tropicalis, 1	Rheumatoid arthritis, 7 (35%) Crystal induced arthritis, 5 (25%) Spondyloarthropathy, 2 Osteoarthritis, 2 (10%) Reactive arthritis, 2 Fracture or postoperative, 2

Table-2: Details of nine tuberculous arthritis patients.

Age/Sex	Comorbidities	SF-ADA (U/L)	Involved joint	Diagnostic evidence	Improved with anti-TB therapy?
66/M	DM, ESRD	250	Elbow, right	Culture, PCR	Yes
85/F		103	Shoulder, left	Culture, PCR	Yes
61/F	DM, HTN, ESRD	76	Knee, left	Culture	NA
55/M	Pul. TB	108	Shoulder, left	Culture, PCR	Yes
38/M	Pul. TB	84	Knee, right	PCR	Yes
78/F	RA, NSIP	78	Knee, right	Culture	Yes
58/M	HTN	219	Knee, right	Culture, PCR	Yes
58/F	Dermatomyositis	195	Hip	Culture	Yes
61/M	Psoriasis, CKD, HTN TB spondylitis	199	Wrist, left	Culture, PCR	Yes

SF-ADA, synovial fluid ADA; DM, diabetes mellitus; ESRD, end stage renal disease; HTN, hypertension; Pul TB, pulmonary tuberculosis; RA, rheumatoid arthritis; NSIP, nonspecific interstitial pneumonitis; CKD, chronic kidney disease.

tuberculosis, positive polymerase chain reaction (PCR) for M. tuberculosis, and histologic evidence of tuberculosis. All patients diagnosed with TB arthritis were treated with anti-tuberculosis drugs and improved in various sequelae, with the exception of one patient who died from cardiovascular problems. All synovial fluid from the non-TB septic arthritis samples grew microorganisms other than M. tuberculosis. Non-infectious arthritis was confirmed by rheumatologists and orthopaedic surgeons.

Because the data were not normally distributed by a Shapiro-Wilk test, ADAs were compared using nonparametric Kruskal-Wallis and Mann-Whitney tests with Bonferroni correction. The results are presented as median with range. A p-value < 0.05 was considered significant. All analyses were performed using SPSS version 22.0 for Windows and MedCalc version 15.0.

ADA test performed during the study period showed 9 out of 11 patients with TB arthritis, 14 with non-TB septic arthritis, and 20 patients with non-infectious etiology. The knee joint was the most frequently involved part of the body in all categories of patients. Staphylococcus aureus was a major cause of pyogenic arthritis 10 (71%) and one patient had candida arthritis of the knee. In non-infectious arthritis, 60% (12/20) of the cases were rheumatoid arthritis (35%, 7/20) or crystal-induced arthritis (25%, 5/20) (Table-1). The characteristics of the nine patients with TB arthritis are described in Table-2. Two of the nine patients with TB arthritis had pulmonary tuberculosis and one had tuberculous spondylitis simultaneously. One patient died before the start of anti-tuberculous treatment because of underlying cardiovascular problems. Eight of nine patients had AFB cultures with growth after three to eight weeks, and three were

negative, based on PCR, for tuberculosis (Table-2).

The mean ADA level in TB arthritis, non-TB septic arthritis, and non-infectious joint fluid was 108 (range, 76-250) U/L, 119.8 (range, 23-250) U/L, and 31.5 (range, 11-60) U/L, respectively. According to the manufacturer, the upper detection limit of ADA was 250 U/L. In this study, all ADAs were ≤60 U/L in non-infectious synovial fluids and ≥76 U/L in TB arthritis (Figure). Non-infectious inflammatory synovial fluids can be clearly distinguished from TB arthritis using a synovial ADA cut-off value of 60-76 U/L (dashed lines in Figure). Although ADAs in non-infectious joint fluids were significantly lower than ADAs in non-TB septic arthritis ($p < 0.001$), but five out of 14 patients (35.7%) non-TB septic arthritis had ADAs level <60 U/L. However, there were no significant differences in joint fluid ADA level between TB arthritis and non-TB septic arthritis ($p = 0.95$)

Discussion and Conclusion

We demonstrated that joint fluid ADA level can be useful for diagnosing TB arthritis and identified a cut-off value of > 60-76 U/L. Foocharoen et al. reported that the mean synovial fluid ADA levels in patients with TB arthritis was 35.7±10.4 (range, 20-51) U/L. They concluded that the sensitivity and specificity for diagnosing TB arthritis were 83.3% and 96.7% respectively, when a cut-off value of 31 U/L was used.[6] However, none of our patients with TB arthritis had synovial ADA values <76 (range, 76-250) U/L. Fujimoto et al. described an adult patient with TB arthritis in the knee joint and indicated that the synovial fluid ADA concentration was 191 U/L.[7] In addition, Sousa et al. showed that the cut-off value of synovial fluid ADA in non-TB prosthetic joint infection was >61 U/L.[8] In contrast, the joint fluid ADA in non-TB septic arthritis was no more than 28 (17-28) U/L in the Foocharoen et al. study. In our report, the median joint fluid ADA concentration in non-TB septic arthritis was 119.8 (range 23-250) U/L. Therefore, previous reports may support the results of our study rather than those of Foocharoen et al. study. However, a concrete conclusion cannot be confirmed because the sample size was very small (n=7 in the Foocharoen et al. report vs. 9 in this study) and both studies were retrospective in design with the inherent limitations. In addition, our report may have a selection bias because not all non-TB synovial samples had joint fluid ADA results during the study period. Nonetheless, the difference between our study and the report by Foocharoen et al. was profound. Therefore, additional prospective studies from various centers are required.

Three patients with TB arthritis showed negative PCR test results for tuberculosis. These patients were diagnosed by AFB cultures, which took three to eight weeks to be reported. While waiting for these AFB culture results, empirical antibacterial therapy was given to the patients, although joint destruction progressed. According to our study results, patients with negative TB-PCR and ordinary bacterial culture results along with high SF-ADA (≥76 U/L) can be treated with anti-tuberculosis medication to prevent devastating joint damage. Therapy can be modified as needed when the AFB culture results are reported.

In conclusion, patients with persistent culture-negative mono- or oligo-arthritis should be considered as possible cases with joint TB. The possible presence of tuberculosis and a cut-off value of SF-ADA 60-76 U/L may be helpful to differentiate TB arthritis from non-infectious causes. Finally, SF-ADA alone should not be used for distinguishing TB arthritis from non-TB pyogenic arthritis.

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Conflict of Interest: None to declare.

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