Comparison of the axillary lymph node between rheumatoid arthritis and psoriatic arthritis with computed tomography

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Abstract

Backgrounds: There is a lack of universally available biomarker to differentiate rheumatoid arthritis (RA) and psoriatic arthritis (PsA).

Purpose: to see if the size of the axillary lymphnodes (ALNs) and the frequency of lymphadenopathy are useful biomarker to differentiate RA and PsA.

Material and Methods: Forty RA and 19 PsA patients without previous biologics usage were retrospectively included. Chest CT was assessed for the presence of lymphadenopathy and the size of the largest ALN. Frequency of lymphadenopathies was statistically compared between RA and PsA. The short axis and the long axis of the largest ALN were also compared and receiver operating characteristic (ROC) curve analysis was performed.

Results: Frequency of axillary lymphadenopathy was significantly higher in RA than in PsA (80% vs 31.6%, $p < .001$). Number of lymphadenopathies in each patient was also significantly higher in RA than in PsA (3.0 vs 1.2 per patient, $p = .005$). Sensitivity and specificity for differentiating RA from PsA by the presence of at least one axillary lymphadenopathy were 0.8 and 0.68, respectively.

The short axis of the largest ALNs in RA was significantly longer than in PsA (6.5 ± 1.6 mm vs 4.7 ± 1.7 mm, $p < .001$). ROC curve analysis of the short axis showed AUC of 0.75 ($p = .002$) and the cutoff value of 5.1 mm with a sensitivity of 0.83 and specificity of 0.74, when differentiating RA and PsA.

Conclusion: Presence of ALN lymphadenopathy and the short axis of the largest ALN may have a potential utility in differentiating RA and PsA.

Keywords

joints, inflammation, CT-quantitative, rheumatoid arthritis, psoriatic arthritis

Introduction

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are the two major arthritis involving peripheral joints. Both arthritis cause irreversible joint deformity which has critical effect on quality of life. Currently, due to the development of disease-specific biologics, a careful selection of medication according to the type of arthritis is encouraged to prevent irreversible joint damage. Consequently, we are

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required to differentiate RA and PsA accurately to provide the best management. However, differentiating these two arthritis is still challenging because typical clinical features are not obvious at an early stage and both arthritis may show similar joint symptoms. Rheumatoid factor (RF) is a useful biomarker which may suggest the presence of RA, but it is known that there are substantial cases of seronegative RA.[1] In addition, over 10% of psoriasis patients can have RF in their serum[2]; therefore, relying overly on the presence of RF may lead to misdiagnosis. Furthermore, although the presence of psoriasis may suggest PsA, 10–15% of PsA have preceding joint symptoms before obvious skin psoriasis, with may also mislead and/or delay diagnosis.[3]

There were several attempts to differentiate the two arthritis at an early stage with imaging investigations, mostly with magnetic resonance imaging (MRI) and ultrasound (US). However, the reported useful findings varied depending on the articles.[4–7] Furthermore, access to the advanced imaging technique and presence of experienced sonographer or radiologists to interpret images may be facility dependent. Hence, a more practical and readily accessible clinical biomarker to differentiate RA and PsA is warranted.

Swelling of the axillary lymph nodes (ALNs) is a common finding in RA. Recently, a study of CT assessment for ALN in RA patients showed a correlation between axillary lymphadenopathy and its disease activity in the hand.[8] On the contrary, the frequency of axillary lymphadenopathy in PsA has not been reported, and the potential utility of ALN to differentiate the two peripheral arthritis has not been studied yet. Previously, it was reported that the use of biologics could alter the size of the corresponding lymphnodes along with the symptom improvement,[9] which makes it difficult to collect the optimal subjects, especially in PsA, because most PsA patients have already been treated with biologics for skin psoriasis before the development of joint symptoms.

In this study, with recruiting bionaive patients which means the patients without the history of biologics usage, we sought to see if the size of the axillary lymphnodes (ALNs) and the frequency of lymphadenopathy may be useful biomarker to differentiate RA and PsA.

Material and methods

This retrospective study was approved by the local institutional ethical board (32–495 (10,588)), and the requirement for written informed consent was waived.

Subjects

We included bionaive RA and bionaive PsA patients, who underwent screening chest CT prior to their initial therapy or therapeutic acceleration to biologics, from January 2018 to December 2020.

By searching medical records, we carefully excluded the following cases: prior usage of biologics; absence of hand symptoms; and presence of concomitant disease which may cause lymphadenopathy, such as acute pneumonia, carcinoma, Sjogren syndrome, breast lesions, and lymphoproliferative diseases. We also excluded cases if the final diagnosis was unconfirmed or when subjects were considered as having both RA and PsA. We calculated the necessary sample size by referring to previous reports, which examined the frequency of axillary lymphadenopathy in RA and spondyloarthritis (SpA).[10] They reported axillary lymphadenopathy was found in 82% of RA and 10% of SpA. Even though SpA is a group of heterogeneous disorders including PsA, we calculated the necessary sample size by using these frequencies because we were unable to find any previous study that showed frequency of axillary lymphadenopathy solely in PsA. Using their frequencies and setting the significant level to 5% on both sides and 1-beta as 0.9, the minimum required sample size was 8.

All RA patients were diagnosed by expert rheumatologists and fulfilled the ACR/EULAR 2010 criteria for RA. All PsA patients were diagnosed by expert dermatologists or rheumatologists and fulfilled the CASPAR criteria.

Clinical data

In addition to gender and age of the subjects, we collected joint symptom duration and data which reflected the systemic disease activities such as white blood cell count (WBC), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), and presence and titer of RF (positivity >15 IU/ml). Positivity and titer of anti-cyclic citrullinated peptide antibody positivity (ACPA) (positivity >4.5 U/mL) were also obtained in RA group. In PsA group, the duration of skin psoriasis was recorded. Blood test and CT were taken within a month.

Chest CT and image analysis

CT images were acquired by using SOMATOM Definition Flash (Siemens Healthcare, Forchheim, Germany). The scan parameters were as follows: large bowtie filter, 120 kV, 200 mA; 0.5 s exposure time; pitch 1.2; and detector acquisition configuration was 0.6 ×128 mm. The CARE Dose 4D system performs automatic tube modulation according to the patient's size and X-ray attenuation changes along with real-time tube current modulation during each tube rotation. All images were reconstructed on the transverse plane at slice thickness of 5.0 mm, and a I30-reconstruction kernel. The display field of view (FOV) was adjusted so that each body size was isometric on the monitor screen. Raw data were reconstructed with the conventional filtered back projection (FBP) algorithm and with the Safire algorithm (value = 3).

Two musculoskeletal radiologists (TF and RK, 10 and 7 years of experience, respectively) independently evaluated all images. Images were annotated and evaluated in random order. We assessed the chest CT with the soft tissue window on picture archiving and communication systems (PACS). Two readers measured ALN bilaterally. We measured the length of soft tissue intensity reflecting the lymph node cortex. Hence, the fat component of hilum was excluded from our measurement (Figure1). We determined the largest lymph node of the subjects by comparing the longest short axis. Hence, one lymph node from each subject was selected for further analysis. The maximum short axis and the maximum long axis of the largest ALN in each subject were recorded. Lymphadenopathy was determined if the short axis of the lymph node was ≥5 mm and the number of lymphadenopathies in each subject was recorded.

For further analysis, consensual results of the presence and the number of lymphadenopathies were made. If discrepancies were found, consensual results were obtained through discussion. As to the short axis and long axis of the largest ALN, two readers' mean length was used as the consensual results.

Statistical analysis

The mean and standard deviation were calculated for numeric variables such as the age, systemic disease activities, and duration of diseases. After analyzing the distribution with the Shapiro–Wilk test, a comparison between RA and PsA was performed by student t-test or Mann–Whitney U test.

Chi-square test was used to compare the number of axillary lymphadenopathy in RA and PsA. The short axis and the long axis of the largest ALNs between RA and PsA were compared using student t-test or Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis and the area under the ROC curve were used to evaluate the short axis and the long axis of ALNs to differentiate RA and PsA. The cutoff value of the short and long axis of ALNs was derived by the Youden index.

To see the interobserver agreement, kappa value and intraclass correlation coefficients (ICC) were calculated. A value less than 0.21 was interpreted as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement, and 0.81 or greater as excellent agreement.

A p-value $< .05$ was considered to indicate statistical significance. Statistical analysis was conducted with SPSS statistics ver 28.0 (IBM).

Results

Patients' characteristics

We excluded 46 cases due to the following reasons: 11 cases with the history of previous biologic usage, 10 cases with

Figure 1. Illustration of the measurement of axillary lymph node (ALN). The straight line showed the length of the short axis of the ALN, and line with arrows showed the length of the long axis of the ALN.

Sjogren syndrome, 1 case with methotrexate (MTX) related lymphoproliferative disease, 1 case with active pneumonia, 3 cases with cancer including one breast cancer, 10 cases because of inconclusive diagnosis or diagnosed as other types of arthritis, 5 cases for the absence of hand symptom, 1 case with diagnosed as having both RA and PsA, 1 case with mammoplasty, and 3 cases due to lack of clinical data. Finally, bionaive 40 RA and bionaive 19 PsA patients were included in this study. The flowchart of the study population is shown in Figure 2, and summary of patients' characteristics of RA and PsA is presented on Table 1. Although MMP-3 was significantly higher in RA than PsA group, other inflammatory markers showed no significant difference between the two groups. Duration of joint symptoms was significantly longer and previous usage of methotrexate was more frequent in RA than in PsA. All PsA patients had psoriasis.

Analysis of ALN in RA and PsA

Figure 3 shows the representative images of RA and PsA patients. The frequency of axillary lymphadenopathy was significantly higher in RA than in PsA (80% vs 31.6%, $p < .001$). Number of lymphadenopathies was also significantly higher in RA than in PsA (3.0 vs 1.2 per patient, $p = .005$). Sensitivity, specificity, and accuracy of the presence of at least one axillary lymphadenopathy as a differencing factor of RA and PsA were 0.8, 0.68, and 0.68, respectively.

The short axis of the largest ALNs in RA was 6.5 ± 1.6 mm, whereas it was 4.7 ± 1.7 mm in PsA, which was significantly different ($p < .001$) (Figure4). On the other hand, the long axis was not significantly different between

RA and PsA (12.4 ± 5.4 mm vs 12.1 ± 4.6 mm, p = .77) (Figure5).

ROC curve analysis of short axis of the largest ALNs showed AUC of 0.75 (p = .002) but AUC of the long axis was 0.47 (p = .77) (Figure6). When RA and PsA were differentiated by the short axis of the largest ALN with the cutoff value of 5.1 mm, the sensitivity and specificity was 0.83 and 0.74, respectively.

Interobserver agreement

Interobserver agreement of the presence of lymphadenopathy, between the two readers, was calculated as kappa value of 0.74 (p < .05), which meant substantial agreement. Intraclass correlation coefficient of the number of lymphadenopathies were 0.83 (p < .05), which was excellent
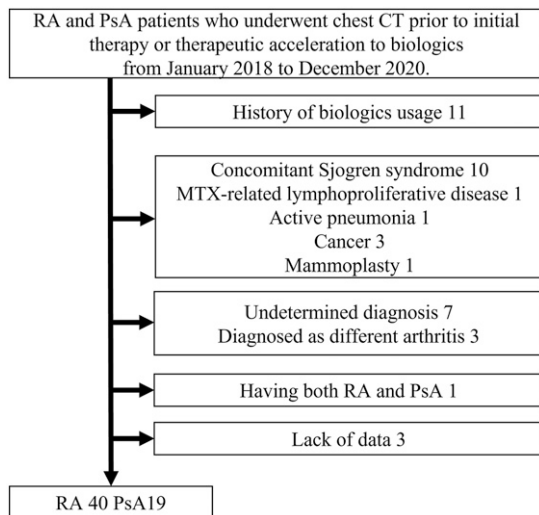

Figure 2. Flowchart showing patient selection.

agreement. As to short and long axis of the largest ALN, ICC was 0.82 (p < .05) which was excellent and 0.72 (p < .05) which was substantial agreement, respectively.

Discussion

We found that the frequency of axillary lymphadenopathy was significantly less in PsA compared to RA. Even though this is a preliminary study with a small sample size, presence of the lymphadenopathy and the short axis of the largest ALN may be a useful biomarker to differentiate the two types of arthritis.

Lymphadenopathy is one of the clinical characteristic features in RA. Along with our result, the frequency of axillary lymphadenopathy was reported as high as 82% in RA.[10] Previously, several imaging studies explored the ALN in RA.[8,9,11] Recent study which measured the size and frequency of axillary lymphadenopathy on CT showed a correlation between ALN and upper limb joint arthritis.[8] Histological changes of lymph node such as reactive follicular hyperplasia, polyclonal plasma cell infiltration in the interfollicular area, and increased germinal centers with high B cell activity were found in RA.[12–15] By incubating ALN of seropositive RA patients with fluorescent agglutinated γ-globulins, RF was found in germinal center localized cells and plasma cells in germinal centers.[16] This finding may explain the unalike reaction of ALN between the seropositive and seronegative RA. However, the recent FDG/PET study did not show any significant difference in metabolic status of ALN between seropositive and seronegative RA.[11] The majority of our RA subjects were seropositive; thus, we were unable to add any further information to this theory. Even though the role of ALN in development and maintaining of RA has not been fully

Table 1. Patients' characteristics.

	RA (n = 40)	PsA (n = 19)	p-value
Gender	M = 11, F = 29	M = 11, F = 8	.02
Age	60.1 ± 16.0	54.3 ± 11.9	.17
WBC (10^3/μL)	7.4 ± 1.9	6.7 ± 2.0	.21
CRP (mg/dL)	2.2 ± 3.5	1.2 ± 2.3	.25
MMP-3 (ng/mL)	233.3 ± 243.4	102.2 ± 64.6	.01
RF positivity	32 (80)	0 (0)	<.001
RF titer	139.5 ± 429.8	0.53 ± 1.6	<.001
ACPA positivity	31 (77.5)	N/A	N/A
ACPA titer	168.2 ± 245.1	N/A	N/A
Duration of joint symptom (months)	41.7 ± 45.7	20.6 ± 54.2	.002
Duration of psoriasis (months)	N/A	34.2 ± 79.8	N/A
Usage of MTX	29 (72.5)	4 (21.1)	<.001

Numbers in parenthesis indicate percentage. RA = rheumatoid arthritis, PsA = psoriatic arthritis, WBC = white blood cell, CRP = C-reactive protein, MMP-3 = matrix metalloproteinase-3, RF = rheumatoid factor, ACPA = anticitrullinated protein antibody, MTX = methotrexate.
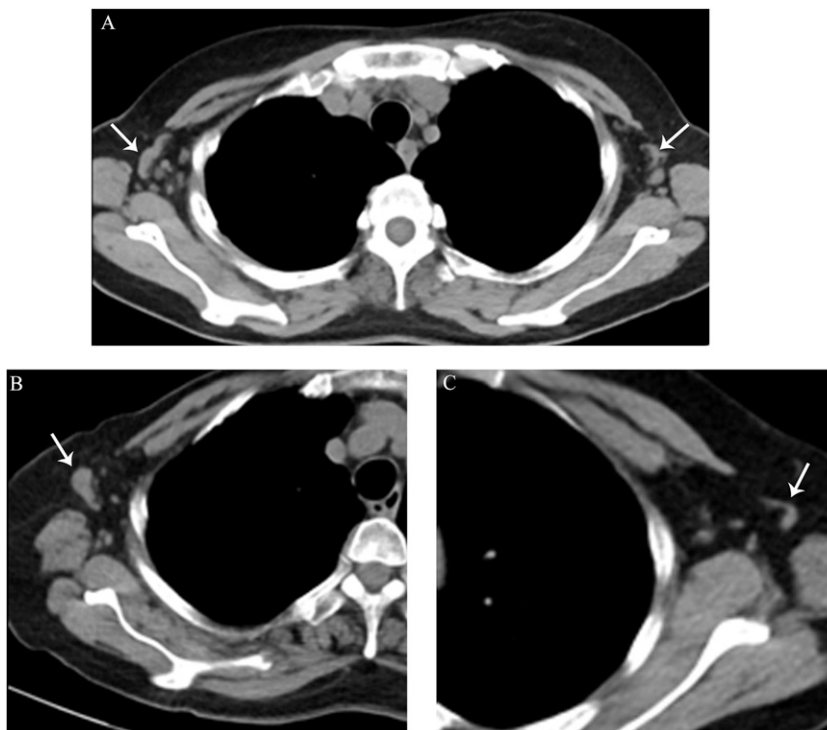
Figure 3. Representative cases showing ALNs in RA and PsA. A Axial chest CT of a 53-years-old female with RA showing bilateral multiple lymphadenopathy (arrow). B Right ALN of a 74-years-old female with RA, showing lymphadenopathy with short axis of 8.1 mm and long axis of 18.9 mm (arrow). C Left ALN of a 73-years-old female with PsA without enlargement (arrow). Length of short axis was 4.5 mm and long axis was 13.6 mm.
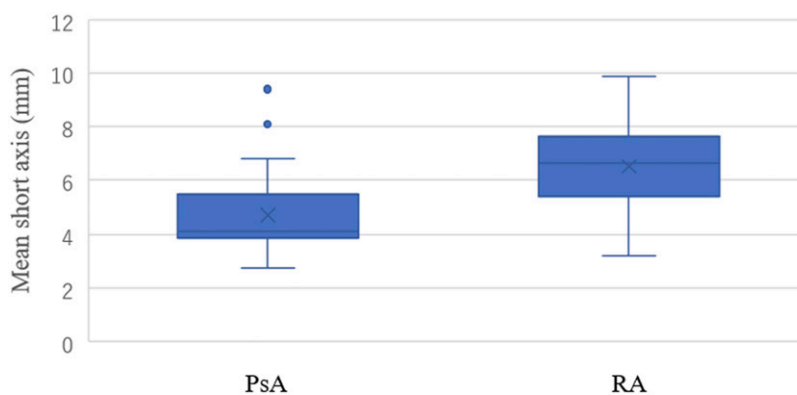

Figure 4. Comparison and distribution of short axis of the largest ALNs between RA and PsA. The average length was 4.7 ± 1.7 mm in PsA and 6.5 ± 1.6 mm in RA, which was significantly different ($p < .001$).

understood, close relationship between axillary lymphadenopathy and RA is well studied.

On the other hand, there are only a few studies that explored the lymph node in PsA, which may imply the rarity of lymphadenopathy in PsA. This includes a study which compared the size of lymphnode among RA, SLE, OA, and SpA including PsA.[10] They assessed the lymphadenopathy with physical examination and found that the frequency of axillary lymphadenopathy was significantly less in OA and SpA than RA and SLE. However, to the best of our knowledge, the direct comparison of ALN with imaging study between RA and PsA has not been conducted yet.

The pathophysiology of RA and PsA has not been fully understood. Even though some overlaps are suggested in the development of inflammatory process of RA and PsA, some important dissimilarities are also reported. From a genetic
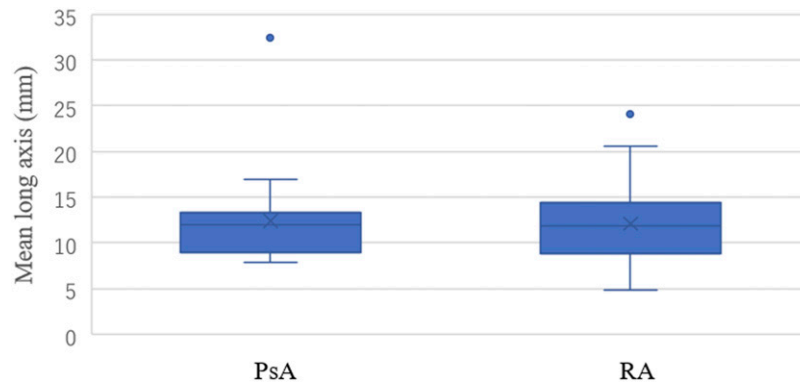
Figure 5. Comparison and distribution of long axis of the largest ALNs between RA and PsA. Average length was 12.4 ± 5.4 mm in PsA and 12.1 ± 4.6 mm in RA, which was not significantly different (p = .77).
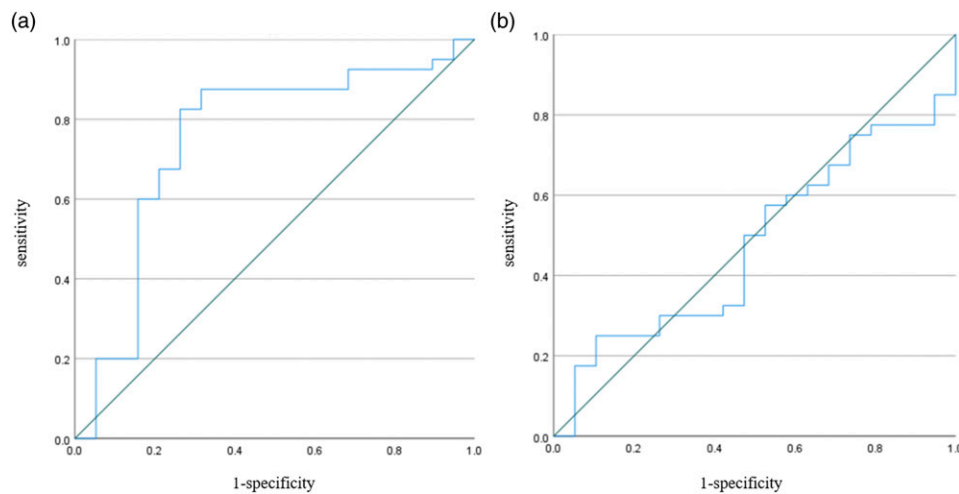

Figure 6. Receiver operating characteristic (ROC) curve analysis. A. Area under the ROC curve (AUC) of short axis of the largest ALNs was 0.75 (p = .002). B. AUC of the long axis of the largest ALNs was 0.47 (p = .77).

aspect, different HLA allele is known to relate in each arthritis.[17] Abnormal production of inflammatory cytokines and chemokines are induced in both arthritis, where interleukin (IL)-23, IL-17, and TNFα pathway are identified as the important pathway for PsA development,[18] and TNFα, IL-6, and IL-1 are identified as the key cytokines in RA.[19] Along with our study, the significant difference in frequency and size of ALN between RA and PsA might be driven by these differences in immunological pathophysiology, regardless of similarities in symptoms in both arthritis.

Assessment of ALN by CT is more reliable than US or clinical examination, but most of the previous reports on ALN assessment in RA were performed by US or clinical examination. If palpation of axillary lymphadenopathy on clinical examination could differentiate RA and PsA, it would be a substantially valuable finding. However, previous breast cancer study showed that the physical

examination as an assessment for the size of ALN, had a low predictive accuracy.[20] US has a better sensitivity in evaluating axillary lymphadenopathy than clinical assessment.[9] However, US is a less objective assessment compared to CT due to its sonographer- and machine-dependence. In this regard, this study used CT and may show a more reliable assessment of ALN, which was reflected by our substantial or excellent interobserver agreement.

History of previous biologics usage is thought to affect the systematic inflammatory status as well as the size of lymph nodes.[9,11] If the study did not exclude the subjects with a medical history of prior usage of biologics, the results might be derived from a heterogeneous population which potentially affect the results. One recent FDG/PET study showed that there is a significant decrease in metabolic status of ALN after biologic therapies.[11] Although this is a retrospective study, through a careful exclusion of patients with a medical history of prior biologics usage, we were

able to compare the ALN of bionaive RA and bionaive PsA subjects. As we expected, collecting bionaive PsA patients was difficult. This is because a substantial number of PsA patients already had a history of biologics usage for skin psoriasis.

This study has some limitations. Firstly, due to its retrospective nature, some disease activity scores such as Disease Activity Score (DAS28) and Health Assessment Questionnaire (HAQ) could not be obtained. Hence, we could not investigate the correlation between these disease activity scores and features of ALN. Radiographic finding do not correlate with disease severity, such as pain in arthritis[21,22]; thereby, we did not correlate severity of hand radiograph and ALN. However, our aim was to investigate the frequency of axillary lymphadenopathy in PsA and evaluate the potential usage of ALN to differentiate RA from PsA. In addition, we can presume that all subjects did have active symptoms because we only included patients who underwent screening chest CT for initial therapy or therapeutic acceleration to biologics. Second, the number of subjects was small and may need to be cautious about the sampling error. As we mentioned before, recruiting bionaïve patients was not easy, especially PsA patients. However, according to the sample size calculation, the number of subjects was sufficient, and we believe that this preliminary study will act as a foundation of further prospective studies. Especially, it is important to further investigate whether ALN is a useful biomarker to differentiate RA and PsA by recruiting more RF-negative RA patients, PsA patients who develops arthritis before psoriasis, and RA with psoriasis.

In conclusion, this study showed that the axillary lymphadenopathy in PsA was less common compared to RA. Also, the presence of lymphadenopathy and the short axis of the largest ALN may have a potential utility in differentiating RA and PsA.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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