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Mediastinal and axillar lymphadenopathy in patients with rheumatoid arthritis: prevalence and clinical significance☆

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ABSTRACT

Background: With recent advances of biological disease-modifying antirheumatic drugs, chest CT has been increasingly performed in rheumatoid arthritis (RA) patients, and mediastinal/axillar lymphadenopathy is being detected.

Purpose: To determine the prevalence of mediastinal and axillar lymph node enlargements on chest CT in RA patients at the initial diagnosis, and to assess its clinical significance.

Material and methods: We retrospectively reviewed the medical records and chest CT findings of 78 consecutive RA patients. The short axis of the most enlarged lymph nodes (SLN) on CT was measured for the mediastinal and axillar regions separately. The SLN was classified into two groups: Group 1, 10 mm or less; and Group 2, larger than 10 mm.

Results: Group 2 was observed in 13 of 78 patients (17%) for the mediastinum, and in 29 (37%) for the axilla; 11 patients (14%) showed Group 2 for both regions. The Group 2 patients (n = 31), either mediastinum or axilla, showed significantly higher simple disease activity index (SDAI) (mean, 36.0) than the patients of Group 1 (n = 47; mean SDAI, 23.0) ($p < 0.001$). For the mediastinal SLN, the RA-related lung disease was more frequently observed in the Group 2 patients than in the Group 1 (p = 0.036).

Conclusion: The mediastinal and/or axillar lymphadenopathy on chest CT may reflect the activity of RA. The mediastinal lymphadenopathy also seems to relate to the RA-related lung disease.

1. Introduction

Rheumatoid arthritis (RA) is a common systemic disease that manifests as inflammatory arthritis of multiple joints and produces lymphadenopathy and a wide variety of intrathoracic lesions including diffuse interstitial pneumonia and bronchitis/bronchiolitis [1]. The presentation of the disease and the course over time is highly variable both within as well as between individuals [2]. Outcome of RA patients depends to a large extent on disease activity, and RA-related lung disease is the most common cause of death (18%) of RA patients next to infection [3–6].

Over the last 2 decades, there has been a paradigm shift in the treatment of RA. Biological disease-modifying antirheumatic drugs (DMARDs) are recent options for RA disease management that may facilitate the prevention of joint damage and disease progression. RA patients are frequently on immunosuppressants, which may predispose them to drug-related toxicity and opportunistic infections of the lung. With recent advances of biological DMARDs, chest CT has been increasingly used in RA patients before the initiation of antirheumatic therapy, and mediastinal and axillar lymphadenopathy is being detected.

Although there were several physical examination reports of lymphadenopathy in RA patients [7–9], CT reports of this association have been limited [10,11]. Moreover, to our knowledge, no study has previously investigated the frequency of mediastinal and axillar lymphadenopathy on chest CT in RA patients before the initiation of antirheumatic therapy and its clinical significance. The purpose of this study was to determine the prevalence of mediastinal and axillar lymph node enlargements on chest CT in RA patients at the initial diagnosis, and to assess the correlation between them and disease activity.

☆ There is no actual or potential conflict of interest in relation to this article.

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2. Materials and methods

2.1. Patients and disease activities

We retrospectively reviewed the medical records and chest CT findings of 78 consecutive RA patients (16 men; mean age, 58.8 years ± 16.5 [standard deviation], 62 women; mean age, 58.3 years ± 13.5, age range, overall mean age, 58.4 years ± 14.0), who met the following criteria; (a) having fulfilled the 2010 American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) diagnostic criteria [12], (b) having undergone chest CT at initial diagnosis of RA, (c) having no other autoimmune disease (eg. Sjögren syndrome, systemic sclerosis, dermatomyositis), (d) having no other active lung inflammation and malignancy. Disease activity was assessed by the simple disease activity index (SDAI), which is the numerical sum of the following five parameters: tender and swollen joint count, patient and physician global assessment of disease, and level of CRP [13]. Five patients had low activity (SDAI; > 3.3 and equal to or < 11), 40 had moderate activity (SDAI; > 11 and equal to or < 26), and 33 had high activity (SDAI; > 26).

Our institutional review board approved this study and informed consent was waived.

2.2. CT scanning protocol

Whole lung was scanned with a 16-, 32- or 64-detector row CT (Aquilion 16, 32 or 64, Toshiba Medical Systems) by using the following technique: 2.0 mm section width with 2.0 mm reconstruction interval, pitch (ratio of table travel per rotation to total beam width) of 15, 120 kVp, 300 mA. Automatic tube current modulation (z-axis modulation with Real E.C. technique, Toshiba Medical Solutions) was used with the noise level set at 10 SD.

2.3. CT image analysis

All images were reviewed on an ultra-high-resolution gray-scale monitor (Coronis3MP, 20.8-in. 2048 × 1560-pixel; BARCO Display Systems, Kortrijk, Belgium) using a standard lung window (window width, 1600 HU; window level, −600 HU) and mediastinal window (window width, 350 HU; window level, 50 HU). The short axis of the most enlarged lymph nodes (SLN) was measured for the mediastinal and axillar regions separately by one general radiologist with 8 years of experience. The SLN was classified into two groups: Group 1, 10 mm or less and Group 2, larger than 10 mm for both the mediastinum and axilla. We defined the Group 2 as lymphadenopathy positive [14]. Two chest radiologists with 25 and 11 years of experience evaluated the lung CT findings for RA-related lung disease (interstitial pneumonia and bronchitis/bronchiolitis). They coded as present or absent separately, and the final decision was reached by consensus when different.

2.4. Statistical method

The relationship between the SDAI for RA and the SLN and the correlation between RA-related lung disease and the SLN was evaluated with non-parametric Mann–Whitney *U* test. All statistical analyses were performed with StatView 5.0 (SAS Institute). The *P* values < 0.05 were considered statistically significant. Interobserver variability for the RA-related lung disease on CT was calculated as a weighted κ value. The strength of agreement was considered fair for κ values of 0.21–0.40, moderate for κ values of 0.41–0.60, good for κ values of 0.61–0.80, excellent for κ values of 0.81 or greater.

3. Results

Group 2 was observed in 13 of 78 patients (17%) for the mediastinum, and in 29 (37%) for the axilla; 11 patients (14%) showed Group 2 for both regions. The difference in SDAI between the two groups according to the SLN was significant ($p < 0.001$). The Group 2 patients ($n = 31$), either mediastinum or axilla, showed significantly higher SDAI (mean, 36.0) than the patients of Group 1 ($n = 47$; mean SDAI, 23.0) ($p < 0.01$) (Figs.1 & 2).

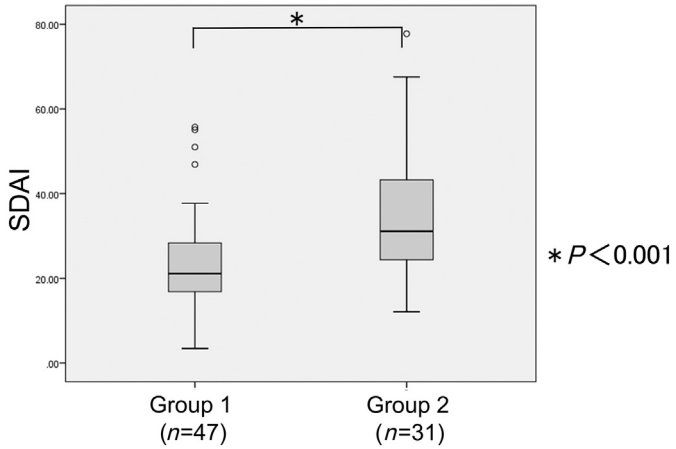

Fig. 1. Simple disease activity index of 2 groups according to the mediastinal/axillar lymphadenopathy.

RA-related lung disease was observed in 28 of 78 patients (36%). The κ value for the RA-related lung disease between 2 radiologists was excellent (κ = 0.89). For the mediastinal SLN, the RA-related lung disease was more frequently observed in the Group 2 patients (8 of 13; 62%) (Figs.3 & 4) than in the Group 1 (20 of 65; 31%) ($p = 0.036$). For the axillar SLN, there was no difference between two group regarding the RA-related lung disease ($p = 0.37$).

4. Discussion

Lymphadenopathy in autoimmune diseases is accompanied by paracortical hyperplasia with prominent vascular proliferation. The lymph node vasculature plays critical roles in delivering immune cells as well as oxygen and micronutrients [15]. Nosanchuk and Schnitzer reviewed the histologic studies of thoracic nodes in 21 patients dying of RA and identified an abundance of plasma cells in the interfollicular zone of the nodes removed at autopsy [16]. Vascular proliferation may lead to plasma cell infiltration in the interfollicular area, resulting in lymphadenopathy in RA patients.

CT reports of lymphadenopathy in RA patients are few [9,10]. Tanaka et al. investigated the prevalence of lymph nodes > 10 mm in 61 RA patients on CT, and mediastinal lymphadenopathy was found in

Fig. 2. Group 2 patient without RA-related lung disease. CT shows bilateral axillary lymphadenopathy (arrows). In this case, mediastinal lymphadenopathy was not observed and SDAI was 61.2, which indicates high disease activity (SDAI; 26 <).

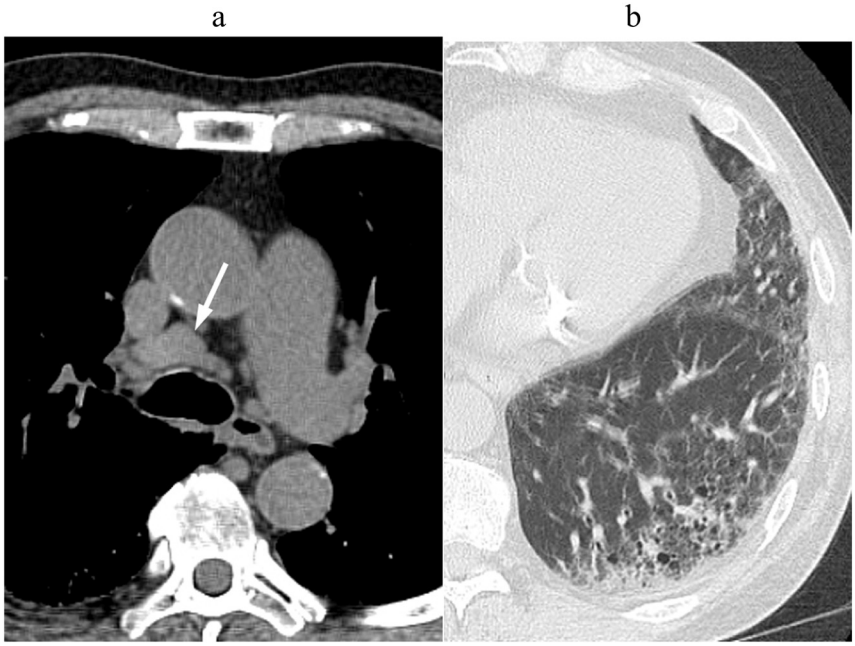

Fig. 3. Group 2 patient with RA-related lung disease. Enlarged mediastinal lymph node (a) (arrow) and interstitial pneumonia with traction bronchiectasis (b) are shown on CT images. In this case, SDAI was 25.4, which indicates moderate disease activity (SDAI; 11 < to 26).

20% of their series. In this study, lymphadenopathy was observed in 17% for the mediastinum [10]. Given the moderate sample sizes of the two studies, there is no substantial difference between 17% and 20%. The other is that 11 of the 13 patients with enlarged mediastinal lymph nodes had enlarged axillary lymph nodes. This may suggest that it is less common to have enlarged mediastinal lymph nodes without enlarged axillary nodes but not vice-versa.

The patients with lymphadenopathy, either mediastinum or axilla, showed significantly higher SDAI than the patients without lymphadenopathy. The SDAI is a valid and sensitive assessment of disease activity of RA patients, and therefore lymphadenopathy may reflect an immune response in RA patients. Radiologists tend to pay attention for the presence of pulmonary pre-existing inflammatory change and interstitial pneumonia on chest CT in RA patients at the initial diagnosis, and may fail to report lymphadenopathy. We believe that radiologists should be aware of the relationship between the lymphadenopathy and the disease activity of RA.

Although the lymphadenopathy in RA patients is mostly part of an inflammatory process, superimposed malignant process needs to be ruled out. When cases of lymphadenopathy on CT in RA patients are encountered, the relationship between the lymphadenopathy and the disease activity of RA should be taken into consideration for differentiation of them. Radiologists need to know the prevalence of the lymphadenopathy observed on chest CT in RA patients as well as the relationship between the lymphadenopathy and the disease activity of RA.

Although generalized lymphadenopathy has been described in RA patients, the enlarged nodes are often located near the inflamed joints [9]. Because the hands are the earliest and most common site in RA patients, the axillary area is particularly affected. Axillary lymph nodes drain the upper extremity and thus likely reflect disease activity in the hand and wrist. Similarly, mediastinal lymph nodes drain the lung. In this study, patients with mediastinal lymphadenopathy showed significantly higher incidence of RA-related lung disease, but no difference in axilla. It is possible that the development of mediastinal lymphadenopathy was facilitated by the combination of RA-related lung disease.

This study is inherently limited by its retrospective nature with a study group of 78 patients. Additional prospective study with a large number of cases, including time course, would be necessary to clarify whether the lymphadenopathy allows for potential therapeutic monitor

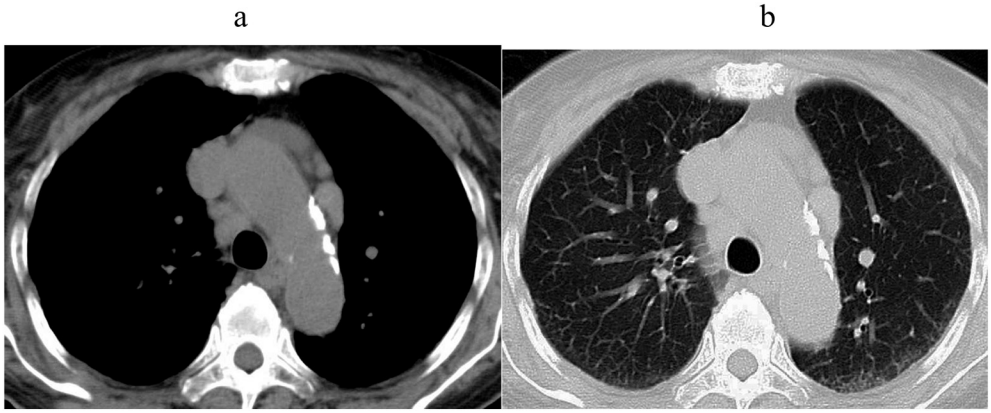

Fig. 4. Group 2 patient with RA-related lung disease. Enlarged mediastinal lymph nodes (a) and interstitial pneumonia showing peripheral ground-glass opacity (b) are shown on CT images. In this case, SDAI was 35.9, which indicates high disease activity (SDAI; 26 <).

or not. Another limitation is that pathologic confirmation was not available. Correlation between CT and histopathologic findings would clarify the pathogenesis of the lymphadenopathy in RA patients. The other limitation is that this study population comprised sequential RA patients who underwent chest CT. This may reflect a relatively sicker/more complicated RA population than the overall RA population.

In conclusion, mediastinal and/or axillar lymphadenopathy on chest CT may reflect the disease activity. The mediastinal lymphadenopathy also seems to relate to the RA-related lung disease.

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