

Rheumatoid arthritis coexisting with ankylosing spondylitis

A report of 22 cases with delayed diagnosis

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Abstract

Coexisting rheumatoid arthritis (RA) and ankylosing spondylitis (AS) in the same patient is often thought to be rare, and thus misdiagnosis is common. The aim of our study was to describe the main characteristics of RA coexisting with AS in patients with delayed diagnoses and improve awareness of the disease association.

Between 2012 and 2018, data from 22 patients who had RA and AS (RA/AS) were retrospectively reviewed. All patients had a history of delayed diagnosis for RA or AS. The clinical features and radiographic changes of RA and AS patients were obtained at baseline and after 2 years. Disease activity score 28 (DAS28) or bath ankylosing spondylitis disease activity index (BASDAI) were used as outcome measures. The mean age at the time of diagnosis of RA/AS was 51.8 years, while the mean duration of diagnostic delay was 5.5 years. Middle-aged women were the most common subgroup among the RA/AS cohort. The common clinical manifestations were systemic, symmetric, peripheral, and axial arthritis. The erythrocyte sedimentation rate and C-reactive protein levels in RA/AS patients were elevated at the time diagnosis of RA/AS. The typical radiologic changes for the 2 diseases coexisted in RA/AS patients. The DAS28 and BASDAI scores at the 2-year follow-up evaluation were lower than the initial assessment.

Coexisting RA and AS is often misdiagnosed for many years; a lack of recognition of RA and AS together is one of the most common reasons. Systemic, symmetric, peripheral, and axial arthritis in middle-aged women were the most frequent presentations at onset.

Abbreviations: AS = ankylosing spondylitis, BASDAI = bath ankylosing spondylitis disease activity index, DAS28 = disease activity score 28, RA = rheumatoid arthritis.

Keywords: ankylosing spondylitis, coexistence, diagnosis, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are common autoimmune rheumatic diseases that have obvious distinctions in genetic peculiarities, clinical manifestations, imag-

ing features, and serologic markers. According to previous reports, the 2 diseases rarely coexist in the same patient^[1-3]; however, we found that patients with coexisting RA and AS (RA/AS) are not rare in the clinical setting. Thus, it is possible that a large number of these patients are overlooked by clinicians. To improve the early diagnosis and treatment, we retrospectively analyzed 22 RA/AS patients with delayed diagnoses over the past 7 years.

2. Methods

2.1. Patients

From January 2012 to December 2018 patients who were diagnosed with RA and AS at the Affiliated Hospital of Qingdao University were identified using a computer retrieval system. Patients who had complaints of a delayed diagnosis for either disease were collected. The protocol was reviewed and approved by the local Ethics and Research Committees of the Affiliated Hospital of Qingdao University.

2.2. Inclusion criteria

According to medical records, RA was diagnosed using the 1987 American Rheumatism Association classification criteria^[4] and AS was diagnosed using the 1984 revised New York standard.^[5] Patients with psoriasis or a family history were excluded from this study. Patients with RA associated with other connective tissue diseases were also excluded.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2.3. Clinic and laboratory data

Clinical data, including age, sex, duration of disease, family history, number of swollen and tender joints, and extra-articular manifestations (EAMs), were collected from medical records. EAMs included rheumatic nodules, rheumatic vasculitis, xerophthalmia, iridocyclitis, infection, lung involvement, cardiac involvement, nervous system lesions, and anemia.^[6–8] The laboratory examination included a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, rheumatoid factor (RF) titer, and anti-cyclic citrullinated peptide (anti-CCP), anti-nuclear (ANA), and human leukocyte antigen-B 27 (HLA-B₂₇) antibody titers. Use of disease-modifying anti-rheumatic drugs (DMARDs) and biological agents was recorded.

2.4. Imaging

Two imaging experts concurrently reviewed the imaging x-ray data of the hands and wrists and computed tomography (CT) data of the sacroiliac joints (SIJs) and lungs from the 22 patients. Scores of space narrowing and bone erosion were obtained at baseline and after 2 years according to the Sharp method.^[9,10] Radiographs of the SIJ obtained at baseline and after 2 years of follow up were scored according to the modified New York criteria grading system (grade 0–4)^[11]; however, we did not perform a statistical analysis for imaging changes due to the small sample size.

2.5. Follow-up and assessment

The disease activity score (DAS28) score and the Bath ankylosing spondylitis disease activity index (BASDAI) were used to assess disease activity.^[12,13] DAS28 scores were assessed at the first rheumatology visit and after 2 years of follow-up.

2.6. Statistical analysis

All statistical analyses were performed with SPSS (version 25.0; IBM, Armonk, NY). The $\bar{X} \pm S$ was used to represent the normal distribution of metrological data and medians were used to represent non-normally distributed data. Frequencies and rates were used to represent count data.

3. Results

3.1. Demographics and laboratory data

Thirty patients who were diagnosed with RA and AS were identified. Twenty-two patients (73.3%) who had history of delayed diagnosis for either disease were included in this study. The mean age of RA/AS patients was 51.80 ± 18.20 years. The mean duration of diagnostic delay was 5.5 years. The male-to-female ratio was 1: 2.14. At the time of the initial diagnosis of RA/AS, the average leukocyte count, hemoglobin concentration, platelet count, ESR, CRP level, and RF and anti-CCP antibody titers were 8.18 ± 2.84 ($\times 10^9/L$), 118.00 ± 22.00 (g/L), 336.00 ± 107.00 ($\times 10^9/L$), 81.25 ± 97.20 (mm/60 min), 67.70 ± 65.74 (mg/L), 114.08 ± 193.10 (IU/mL), and 148.60 ± 185.33 (U/mL), respectively. The positive titers for HLA-B₂₇, and ANA antibody titers were 57.10% (12/21), and 40.90% (9/22), respectively (Table 1).

3.2. Imaging

We quantified the hand and double wrist x-ray grading (0–5) and SIJ x-ray and CT grading (0–5) of patients with coexisting RA

Table 1

Clinical data and disease activity assessment and follow-up data of the patients with coexisting RA and AS.

RA/AS (n=22)	Clinical data at the first rheumatology visit	Disease activity assessment and follow-up data after 2 years
Age, y	51.80 ± 18.20	
Proportion of gender	1.00: 2.14	
Course of disease, y	10.50 ± 10.70	
Family history	9/22	
ESR (mm/60 min, range 0–20)	81.25 ± 97.20	
CRP (mg/L, range 0–5)	67.70 ± 65.74	
RF (IU/mL, range 0–20)	114.08 ± 193.10	
Anti-CCP (U/mL, range 0–17)	148.60 ± 185.33	
The count of hemoglobin (g/L, range 120–160)	118.00 ± 22.00	
The count of leukocytes ($\times 10^9/L$, range 4–10)	8.18 ± 2.84	
The count of platelet ($\times 10^9/L$, range 100–300)	336.00 ± 107.00	
The positivity rate of ANA antibody (%)	40.90 (9/22)	
The positive rate of HLA-B27 antibody (%)	57.10 (12/21)	
The DAS28 scores	5.98 ± 0.94	4.04 ± 1.25
The BASDAI scores	9.13 ± 0.59	5.44 ± 1.12

AS = ankylosing spondylitis, BASDAI = bath ankylosing spondylitis disease activity index, DAS28 = disease activity score 28, HLA-B₂₇, human leukocyte antigen-B 27, RA = rheumatoid arthritis.

and AS. The typical radiologic changes of the coexisting diseases in 2 RA/AS patients are shown in Fig. 1. Imaging classification is shown in Table 2.

3.3. Changes in disease activity after 2 years of follow-up

The mean values of the DAS28 and BASDAI scores at the initial rheumatology diagnosis were 5.98 ± 0.94 and 9.13 ± 0.59 , respectively. After 2 years of follow-up, the mean values were 4.04 ± 1.25 and 5.44 ± 1.12 , respectively. The DAS28 and BASDAI scores of the 2-year follow-up were lower than the first assessment (Table 1). One patient was lost to follow-up and 1 patient died.

3.4. Treatment

The 22 patients were treated with at least one of the DMARDs during the 2-year follow-up. Methotrexate was most commonly used (14/22), followed by sulfasalazine (12/22), leflunomide (10/22), hydroxychloroquine (6/22), and thalidomide (3/22). Notably, 18 of 20 patients used at least one TNF inhibitor for >6 months including etanercept, adalimumab, and infliximab.

4. Discussion

RA and AS occur with comparable frequencies (0.30%–1.50%) in the general population. The probability for co-occurrence of RA and AS in the same patient has been reported to range from 1/50,000 to 1/100,000.^[14,15] However, the rarely described phenomenon of RA and AS coexistence may be more widespread than previously thought because of some uncertain genetically conditions or administered therapy which can mask the symptoms of one of the diseases.^[1] In our study we identified 30 RA/AS patients; 22 (73.3%) patients had a history of delayed diagnosis for RA or AS. The mean duration of diagnostic delay was 5.5 years. This implies that misdiagnosis or diagnosis delay may be another reason for the rarely described phenomenon of

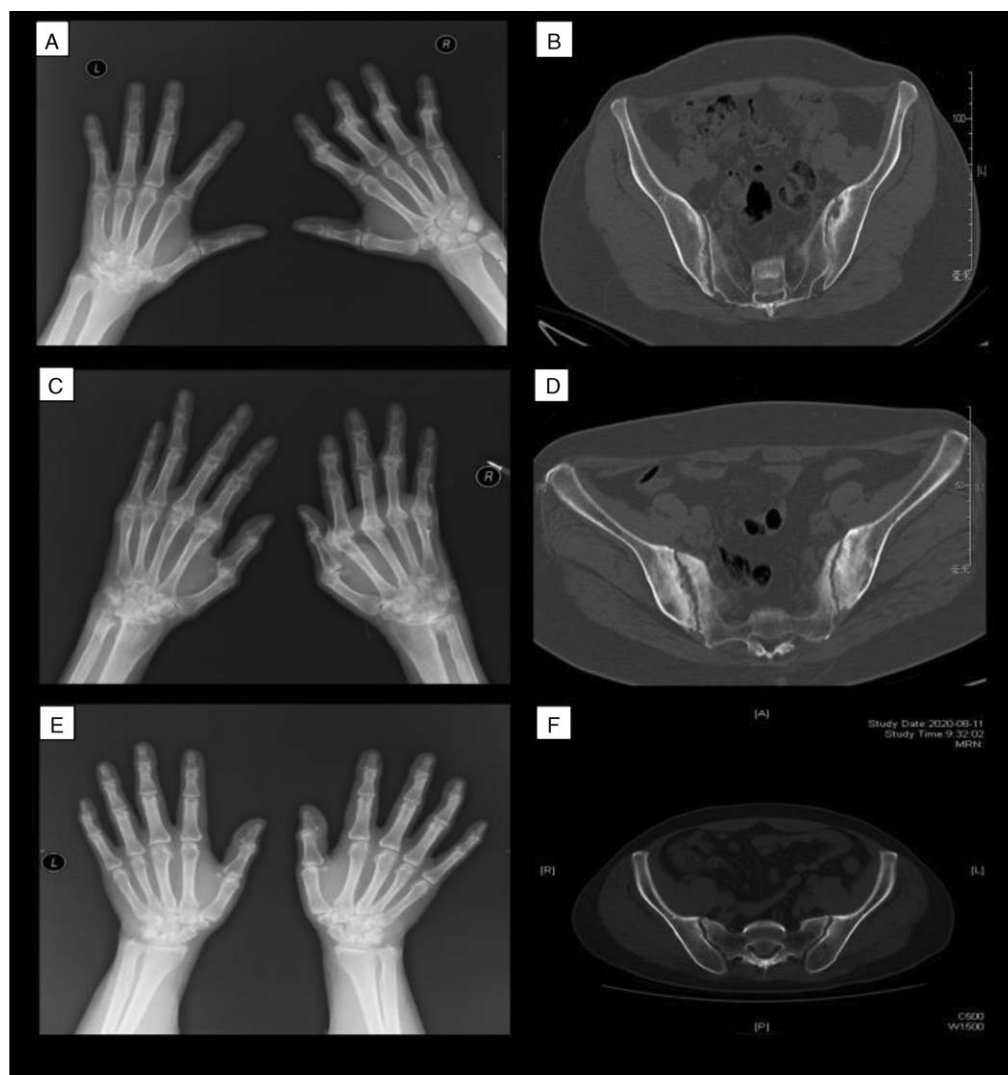


Figure 1. Radiographic features of 2 RA/AS patients. Patient 1: The hand x-ray in Panel A shows subluxation and inflammatory changes with erosions in the right PIP joints, destructive changes indicative of ankylosis in the left wrist. The CT radiograph of SIJs in Panel B shows bilateral sacroiliitis and bone erosions. Patient 2: The hand x-ray in Panel C shows subluxation, erosions, and joint space destructive changes in the right MCP joints, bone erosions in both PIP joints, destructive changes indicative of ankylosis in both wrist. The CT radiograph of SIJs in Panel D shows bilateral sacroiliitis, bone erosions, and joint space destructive changes. Panel E: normal x-ray of the hands and wrists. Panel F: normal CT of the SIJs. AS=ankylosing spondylitis, CT=computed tomography, MCP=metacarpophalangeal, PIP=proximal interphalangeal, RA=rheumatoid arthritis, SIJs=sacroiliac joints.

coexistence of the 2 diseases. In the context of the current study, there might be several reasons for the diagnostic delay. First, some AS patients have no prominent axial symptoms; thus, peripheral arthritis could lead to a diagnosis of RA. Similarly, RA patients are seldom screened for HLA-B₂₇ antibodies or undergo a SIJ x-ray examination.^[16] Third, some RA/AS patients were RF- and HLA-B₂₇-negative, which is often overlooked by clinicians. Our study suggested that vigilance and careful clinical examinations that include essential tests should facilitate early recognition in patients with these 2 chronic conditions. Particular attention should be paid to RA patients with symptoms of typical axial spondyloarthritis, as well as AS patients with symptoms of peripheral joint arthritis. AS is more commonly seen in young male adults; however, our study showed that most RA/AS patients with a delay in diagnosis were middle-aged women. This finding showed that there is a need for an awareness of coexisting RA and AS in middle-aged women.

One of the common features of the 2 diseases is the increase of inflammatory markers like CRP and ESR, which are both elevated significantly in our patients. At the same time, HLA-B₂₇ and RF, 2 markers that could have distinguish the 2 diseases, exist simultaneously in 12 patients. According to previous studies, one-half of AS patients have peripheral joint involvement at some stage of the disease that may be indistinguishable from RA, both clinically and pathologically.^[17,18] Similarly, patients with advanced RA can have bony fusion of the cervical spine and SIJs that is radiologically indistinguishable from AS.^[19,20] Our study demonstrated that the typical radiologic changes of the 2 diseases can coexist. For example, as seen in 10 patients, bilateral sacroiliac and lumbar vertebrae damage, including “bamboo-like” changes, can coexist with symmetric small joint damage. The primary manifestation based on lung computed tomography in the RA/AS group was pulmonary interstitial fibrosis. Other manifestations included pulmonary infections, lung fibrous foci,

Table 2
Imaging classification of the patients with coexisting RA and AS.

	RA/AS (n=22)
Sharp scores	63.00 ± 47.00
X-ray classification of hand joint and wrist joint (%)	0 level 11.00 (1/9) 2 level 33.00 (3/9) 3 level 22.00 (2/9) 4 level 33.00 (3/9)
CT classification of sacroiliac joint (%)	2 level 13.60 (3/22) 3 level 72.70 (17/22) 4 level 13.60 (3/22)
Involvement of pulmonary by CT (%)	86.40 (19/22)
Involvement of cervical vertebrae, thoracic vertebrae, or lumbar vertebrae (n of cases)	10
Involvement of shoulder or elbow joint (n of cases)	2
Involvement of knee or hip joint (n of cases)	8

AS=ankylosing spondylitis, CT=computed tomography, RA=rheumatoid arthritis.

pulmonary rheumatoid nodules, pleural thickening, emphysema, pleural effusions, and thoracic hardening; however, we did not perform a statistical analysis of the radiologic changes due to the small sample size.

We assessed the DAS28 and/or BASDAI score(s) at the time of initial diagnosis of RA or AS and after 2 years. We found that after 2 years of therapy, the DAS28 and BASDAI scores of RA/AS patients were lower than the first assessment. All patients had used at least one of the DMARDs and most patients had used at least one TNF inhibitor for >6 months, which might be one explanation for the low disease activity after 2 years of follow-up. The prognosis of our cases is overall good, however, further study is warranted to evaluate the prognosis of this combination compared with the individual disease entities.

The shortcomings of this study were the small number of recruited patients and the retrospective method design. Imaging and treatment information was relatively incomplete. Factors responsible for diagnostic delay like late reporting of symptoms or inadequate imaging have not been further investigated. Long-term or prospective studies are needed for the diagnosis and treatment of RA/AS patients.

In conclusion, the diagnosis of coexisting RA and AS is often delayed. This study encourages rheumatologists to consider RA/AS as a possible diagnosis in patients with both peripheral and axial arthritis. Systemic, symmetric, peripheral, and axial arthritis in middle-aged women were the most frequent presentations at the time of onset.

Author contributions

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