

## Undifferentiated Spondyloarthritis in Korea - Focusing on Peripheral Arthritis -

Undifferentiated spondyloarthritis (USpA) includes the forms that do not meet criteria for the established categories of spondyloarthritis. The clinical spectrum of USpA is therefore wide and few studies have been published on USpA, especially peripheral arthritis. A total of 107 patients fulfilling the European Spondyloarthritis Study Group criteria for SpA were studied retrospectively by a chart review and interview by a rheumatologist. Peripheral arthritis, excluding hip and shoulder involvement, occurred in 97 of the 107 patients (91%). Joint involvement tended to be monoarticular or pauciarticular, and most frequently developed in peripheral joints including the knee and ankle. Among the 97 patients with peripheral arthritis, only 37 (35%) had a persistent arthritis. HLA-B27 was detected in 80 patients (78%). Peripheral arthritis was found in the lower extremities regardless of symmetry or asymmetry and tended to run a benign course with only a few patients having persistent arthritis

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## INTRODUCTION

Spondyloarthritis (SpA) was introduced to describe a family of arthritides of unknown etiology with both peripheral and axial manifestations sharing clinical and radiological features as well as genetic predisposing factors. SpA includes ankylosing spondylitis (AS), Reiter's syndrome and reactive arthritis, psoriatic arthritis, arthritis related to inflammatory bowel diseases, as well as other forms that do not meet the criteria for these categories, called undifferentiated spondyloarthritis (USpA). The clinical spectrum of USpA is therefore wide, due to various combinations of clinical and radiological manifestations of SpA, i.e, inflammatory spinal pain including sacroiliitis, peripheral arthritis, enthesitis, dactylitis, history of diarrhea and urinary tract infection, psoriasis, and uveitis, each of which may also occur in isolation.

Few studies have been published on USpA and peripheral arthritis of USpA, because it has been overlooked in most studies due to inadequacy of the existing classification criteria and misdiagnosis as rheumatoid arthritis. With the use of the recently developed European Spondyloarthritis Study Group (ESSG) criteria (1), the clinical characteristics of USpA may be better defined and may also lead to early recognition of such patients in clinical practice. We retrospectively studied patients with USpA, focusing on the characteristics

and prognosis of peripheral arthritis.

## MATERIALS AND METHODS

### Patients

Among a total of 839 patients with SpA who visited our hospital from 1992 to 1999, 412 had ankylosing spondylitis, 107 had USpA, 17 had psoriatic arthritis, and 10 had reactive arthritis. There was no subject with inflammatory bowel disease. Among these subgroups, a total of 107 patients with USpA were included in this study and analyzed. The diagnosis of USpA was made on those who fulfilled ESSG criteria (1).

### Demographic data

Medical records were reviewed retrospectively and data on age, sex, age at symptom onset, symptom duration, and onset of inflammatory back pain were recorded for all patients. Age at symptom onset was defined as time at which the first symptom, whether it was axial symptom, peripheral arthritis, or enthesitis, had been initially noticed by each patient. Symptom duration was calculated by subtracting the year at symptom onset from 1999.

## Clinical data

Patients were asked about family history (first and second degree relatives) of SpA. All data were recorded about the details of inflammatory back pain, peripheral arthritis, enthesitis, uveitis, history of diarrhea, urinary tract infection, psoriasis, alternative buttock pain, and dactylitis. The determination of current or previous inflammatory back pain was made based on symptoms persisting at least 3 months, improving with exercise and worsening with rest. Peripheral arthritis was defined as the presence of swelling and/or restricted range of motion in at least one peripheral joint, and/or history of previous swelling in at least one peripheral joint confirmed at that time by a rheumatologist (not including hip or shoulder joints) (1). Enthesitis was defined as inflammation and/or pain of peripheral entheses such as in calcaneal insertions of the Achilles tendon and plantar fascia, tibial tuberosities, and costosternal junction. Dactylitis was defined as diffuse digit swelling extending beyond the margin of the joint capsule (2). In peripheral arthritis study, absence of peripheral arthritis and enthesitis was defined as no arthritis and enthesitis for at least 2 months. We identified the characteristics of Korean USpA and the differences in clinical manifestations according to the sex. Also, we carefully analyzed the course of peripheral arthritis in USpA.

## Laboratory data

HLA-B27 by microcytotoxicity and radiological investigations (pelvic and lumbar spine radiographs and radiographs of painful joints and chest) were obtained.

## Statistical analysis

Statistical analysis was performed using the SPSS statistical package. Chi-square test, Fisher's exact test, and t-test

**Table 1.** Demographic and clinical characteristics of the 107 patients

Demographics	Number (%)
Male/female	58/49 (54/46)
Age at onset of disease (yr)	27.4±11.6
Disease duration (yr)	6.3±5.6
Family history of SpA	12 (11)
Uveitis	14 (13)
Microscopic hematuria	9 (8)
Dactylitis	3 (2)
History of urinary tract infection	0
History of diarrhea	0
Psoriasis	0
HLA-B27	80/103 (78)
HLA B7	6/103 (6)
Sacroiliitis	22 (21)

SpA: spondyloarthritis.

for independent values were used as appropriate. *P*-value of <0.05 was regarded as significant. Mann-Whitney U test was performed to identify the correlation between peripheral arthritis and disease duration.

## RESULTS

### Overall outcome

Among the 107 patients with USpA, the male to female ratio was 58:49 (male 54%, female 46%). The mean age at onset was 27.4±11.6 yr (range, 7-58 yr; male, 26.6±13.0; female, 28.3±9.7) and disease duration was 6.3±5.6 yr (range, 3 months-39 yr, male, 6.5±6.4; female, 6.2±4.7). The demographic characteristics are presented in Table 1.

### Initial symptom

The most common initial symptom was arthritis of the knee in 30 patients (28%), ankle in 15 (14%), buttock and axial symptom in 23 (21%), and enthesitis including heel and plantar area in 22 (21%).

### Articular manifestation

A history of peripheral arthritis excluding the hip and shoulder involvement was recorded in 97 patients (91%) in a total of 107 patients. Arthritis involved the knee in 77 of 107 patients (72%). Among the patients with a history of arthritis, both knees were involved in 39 patients (39%), both ankles in 26 (53%), both elbows in 6 (27%), and wrists and hands in 5 (22%) and 4 (16%), respectively. The number of joints involved was one in 12 patients, two in 25 patients, more than 2 and less than 4 joints in 30 patients, and more than 5 joints in 31 patients. The peripheral arthritis was more common in female than in male (98% vs 85%, *p*<0.05). But the pattern of joint involvement was not dif-

**Table 2.** Articular manifestations of Undifferentiated spondyloarthritis

Manifestation	Number (%)
Arthritis	97 (91)
Knee	77 (72)
Ankle	49 (46)
Elbow	6 (27)
Wrist	23 (21)
Hand	25 (23)
Enthesitis	88 (82)
Heel pain	80 (75)
Plantar fasciitis	42 (39)
Tibial tubercle	30 (28)
Chest pain	20 (19)
Inflammatory back pain	58 (54)

ferent between the two groups. The arthroscopic synovectomy of the knee was done in 8 patients. The 88 patients (82%) had enthesitis. The Achilles tendinitis was found in 80 (75%). The 58 (54%) patients complained of inflammatory back pain, 28 patients in hip (26%) and 15 patients in shoulder (14%). Sacroiliitis was diagnosed by pelvis radiography in 22 patients (21%). The arthritic characteristics are summarized in Table 2.

#### Extraarticular manifestations and laboratory findings

Uveitis developed in 14 patients (13%). Microscopic hematuria was found in 9 patients (8%), and biopsy was done in 6 patients thereof, all of whom were diagnosed with IgA nephropathy. Dactylitis developed in 3 patients (2%) and a family history of SpA was found in 12 (11%). No patient suffered from urinary tract infection, diarrhea, or psoriasis. HLA-B27 was done in 103 patients and 80 patients (78%) were positive for HLA-B27.

#### Combination of diagnostic criteria in USpA

The most common combined profile of USpA criteria was peripheral arthritis and enthesitis (48%, respectively). Peripheral arthritis, inflammatory back pain, and enthesitis were observed in 39 patients (36%). Both inflammatory back pain and enthesitis were observed in seven patients. Ten patients had one minor criterion and one of two major factors.

#### Comparisons between the sexes

It was found that peripheral arthritis was the only feature significantly more frequent in women than in men (98% and 85%, respectively;  $p < 0.05$ ). The disease duration did not affect the course of peripheral arthritis.

#### Prognosis of articular manifestation

Sulfasalazine (SSZ) was prescribed in 55 patients, a combination of SSZ and methotrexate (MTX) in 35, and three disease-modifying antirheumatic drugs (DMARDs) including either SSZ or MTX in 7 patients. Ten patients did not receive any DMARDs treatment. Among 97 patients with peripheral arthritis, the arthritis subsided in 60 patients and only 37 (35%) had a continuous peripheral arthritis at follow-up.

Although a history of peripheral arthritis was more frequent in female patients, the difference in persistent arthritis by sex was not statistically significant between two sexes in the long run. Among 88 patients with enthesitis, only 32 (30%) had a persistent enthesitis. The persistence of the peripheral arthritis and enthesitis had no relation with the use of DMARDs.

## DISCUSSION

The SpA is a group of inflammatory arthritic conditions that share certain clinical and laboratory features. The main clinical feature is an inflammatory back pain, which manifests with stiffness in the buttocks and back. Peripheral arthritis may be associated with spondylitis; it is characterized by an absence of rheumatoid factor, hence is designated as seronegative SpA. The arthritic involvement tends to be asymmetric, most commonly in the lower extremities (3).

There have been studies on clinical features of the SpA (2-9). The frequency of USpA is high and the 1:1 male: female ratio has also been observed. The clinical spectrum of USpA is as wide in the elderly as it is in children and young-middle aged adults. However, late onset SpA is uncommon after 55 yr (10) and the pitting edema of the extremities, similar to that of remitting seronegative symmetric synovitis with pitting edema and to that of polymyalgia rheumatica, may be observed (11). Our data shows the similar sex ratio and the disease was not found in patients over 55 yr.

Because few studies have been published on peripheral arthritis in USpA, we have focused on clinical characteristics of USpA and peripheral arthritis in a series of 107 patients. Peripheral arthritis occurred in 91% of our patients. The percentage of peripheral arthritis was similar to those reported in studies conducted by Boyer et al. (8), Mau et al. (9), Prakash et al. (12) and Uppal et al. (13) (range, 52-100%). According to Uppal et al. (13), USpA is frequent in females, tends to involve fewer joints, and there is a greater tendency towards asymmetry in females. Our study has provided an opportunity to evaluate the characteristics of patients with peripheral arthritis that have not been well defined in previous studies. Peripheral arthritis was more frequent in female patients and was not associated with a longer disease duration. Joint involvement tended to be monoarticular or pauciarticular, and regardless of symmetry or asymmetry, the knee and ankle were most frequently involved. The peripheral arthritis was frequent, but not severe.

In India, Prakash et al. (12) reported that in 25 patients attending to a rheumatology clinic with asymmetric seronegative arthritis mainly of the large joints of the lower limbs, associated abnormalities were low back pain (52%), heel pain (28%), sacroiliitis (16%) and mouth ulcer (8%). The patients in this study presented a frequency of lower back pain (54%) similar to that in the study by Boyer et al. However, the frequencies of heel pain and sacroiliitis were higher than those in the study by Boyer et al., showing 82% and 22%, respectively.

Certain extra-articular features are common in USpA, including skin and mucous membrane lesions, bowel complaints, eye involvement, and aortic root dilatation. Boyer et al. (8) reported numerous extra-articular manifestations in 24 Yupik Eskimo patients with USpA; enthesopathy in 56%, mucocutaneous lesion in 16%, genitourinary features like

urethritis, epididymitis, prostatitis, and sterile pyuria in 28%, inflammatory bowel disease in 4%, conjunctivitis or iritis in 33%, cardiac abnormalities (conduction disturbance, pericarditis, and aortic regurgitation) in 8%. In our study, these features were also present: enthesopathy in 82% and uveitis in 13%. However, aortic regurgitation, history of genitourinary features, inflammatory bowel disease, and psoriasis were not found.

Another feature common to SpA is the familial aggregation, which occurs within each condition and among entities within the group. An association with HLA-B27 has been documented in the diseases (14-16). The frequency of HLA-B27 may vary between populations, as shown by two recent studies that reported HLA-B27 positivity in 56% of patients with USpA in an Alaskan Eskimo population and only 6% positivity in a population from Lebanon (17, 18). In Linssen and Feltkamp (19), HLA-B27 positive patients were shown to have an earlier onset of disease, a more severe clinical course, increased frequency of acute anterior uveitis, peripheral arthritis, and increased involvement of the axial skeleton. Frankenberger et al. (20) reported a significantly lower B2702 frequency in patients with USpA (6.7%) than in those with AS (23.7%). In our analysis, HLA-B27 positivity was higher (78%), but no difference in the prevalence of peripheral joint involvement was found between the HLA-B27 positive and the HLA-B27 negative groups.

Clinical findings of the Korean patients with USpA are similar to those of other countries. Peripheral arthritis is a dominant manifestation and tends to run a benign course with only a few patients having persistent arthritis.

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