

Clinical Analysis of Behcet Disease : Arthritic Manifestations in Behcet Disease may present as Seronegative Rheumatoid Arthritis or Palindromic Rheumatism

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Objectives : *To analyze arthritic manifestations in Behcet disease, which is one of the most common manifestations of Behcet disease.*

Methods : *Among the patients who visited the Rheumatology Division, Keimyung University Dongsan Medical Center, Taegu, Korea from March 1997 to February 1998, 35 patients, with more than 3 months follow-up, were compatible for the diagnosis of Behcet disease according to the Shimizu criteria, after exclusion of uncertain or possible Behcet cases. The presence of various manifestations was evaluated. Regarding the joint manifestations, the involved joint, signs and the pattern of the articular symptoms were examined. Basic laboratory tests, HLA studies and simple radiologic studies were done.*

Results : *All 35 patients had evident, recurrent, painful oral ulcers by the study definition. Genital ulcers were found in 29%, skin lesions in 77%, uveitis in 9%, gastrointestinal ulcerations in 6% and vascular manifestations in 6%. Joint manifestations appeared in 97%. Knee (91%), proximal interphalangeal (53%) and metacarpophalangeal joints (21%) were the main sites. Tenderness was prominent in 91% and swelling in 44%. Polyarticular presentation was found in 47%. In most cases (76.4%), the articular symptom was short-lasting. C-reactive protein was likely to be positive in active Behcet disease. HLA B51 was positive in 46%.*

Conclusions : *In Behcet disease, various manifestations can be found. The arthritic manifestation seems quite common. It may present as seronegative rheumatoid arthritis. Otherwise, it may present as palindromic rheumatism.*

Key Words : *Behcet, Arthritis, Seronegative, Rheumatoid*

INTRODUCTION

Behcet disease is characterized by recurrent painful oral ulcer and genital ulcer, skin diseases and uveitis. It may involve cardiovascular, gastrointestinal and central nervous system, as well as joints. The etiology is

unknown and its pathophysiology is incompletely understood. The diagnosis of Behcet disease primarily depends on the patient's history and clinical findings. Arthritic manifestation is one of the minor manifestations and it is usually overlooked. The author analyzed 35 cases of Behcet disease patients, mainly for arthritic manifestations.

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MATERIALS AND METHODS

1. Patients

Among the patients who visited the Rheumatology Division, Keimyung University Dongsan Medical Center,

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Taegu, Korea from March 1997 to February 1998, 52 patients were compatible for the diagnosis of Behcet disease according to the Shimizu criteria¹⁾. Forty seven patients with more than 3 months follow-up were enrolled in this study. Forty three patients were referred to the Rheumatology Division by primary care physicians, two from Department of Ophthalmology and two from General Surgery in Keimyung University Dongsan Medical Center. They had been diagnosed as having Behcet disease by careful history taking, medical record review and thorough physical examination. On initial visit, it usually took more than thirty minutes. All patients were followed-up closely and they visited the hospital every two weeks. A direct telephone number was given to the patients and, whenever they felt uncomfortable with ill-defined symptoms, they discussed with the examiner. The Shimizu criteria were retrospectively and strictly applied again, and five uncertain patients were excluded. Especially, regarding an oral ulcer, only the patients who complained of an evident, recurrent, painful one were included. "Possible" type of five Behcet cases were excluded and two patients, who carried another autoimmune diagnosis (SLE), were excluded, too. Thirty five patients were finally included in this study.

2. Clinical features

The presence of various manifestations were evaluated and recorded as positive or negative. Recurrent aphthous ulceration in the mouth, various skin lesions (erythema nodosum-like eruptions, subcutaneous thrombophlebitis, hyper-irritability of the skin), eye lesions (recurrent hypopyon iritis or iridocyclitis, chorioretinitis) and genital ulcerations were evaluated. The presence of joint manifestations, gastrointestinal and vascular lesions, epididymitis and central nervous system involvements were evaluated too.

They were classified according to the subtypes.

3. Joint manifestations

Arthropathy was defined as arthralgia with the presence of swelling and/or tenderness. Regarding the joint manifestations, the involved joints, tenderness, swelling and the pattern of the articular symptoms were evaluated. The pattern of involvement included the number of involved joints and the duration of arthropathy.

4. Laboratory and radiologic evaluation

Basic laboratory tests, including CBC, erythrocyte

sedimentation rate (ESR, Westergren), C-reactive protein (CRP), complement, immunoglobulin, rheumatoid factor (RF) and antinuclear antibody (ANA), were done. HLA studies were done using Terasaki tray (One Lambda, Inc. U.S.A.). Synovial fluid analysis was tried whenever the patient had sufficient amount of swelling and agreed to aspirate.

Simple radiologic studies of mainly involved joints were done.

5. Comparison with rheumatoid arthritis (RA)

The presence and the duration of morning stiffness, which is relieved by exercise, were also evaluated. The involved joints, tenderness, swelling and the number of involved joints were evaluated, as already mentioned above. RF and simple radiologic studies of mainly involved joints were evaluated again, as already mentioned above, for the purpose of comparing the data with those of rheumatoid arthritis.

The names of the initial diagnosis of the patients with joint manifestations were asked. Regarding oro-genital ulcers or skin lesions, the author asked whether they were asked of the presence of them by their primary care physicians.

RESULTS

1. Patient characteristics

These are shown in Table 1. Mean age was 37 and disease onset was 31. The range of duration between the first clinical manifestation and the diagnosis was from 1 to 25 years. Eighty percent of the patients were female.

Table 1. Characteristics of Patients (n=35)

Age(yrs)	36.6 ± 11.6
Onset Age(yrs)	30.5 ± 10.1
Sex(MF)	7 : 28

Data shown as mean ± SD.

2. Clinical features and interpretation according to the subtype

All 35 patients had evident, recurrent, painful oral ulcers by the study definition. In 46%, they presented as multiple forms. Genital ulcers were found in 29%. Various skin lesions, including erythema nodosum-like eruption,

subcutaneous thrombophlebitis and hyper-irritability of the skin were noted in 77%. Uveitis was evident in 9% of the patients. Joint manifestations appeared in 97%. Gastrointestinal ulcerations and vascular manifestations were found only in 6%, respectively. In vascular manifestations, one patient showed three vascular events (cerebral infarction and carotid, femoral aneurysms). Epididymitis and central nervous system involvement were not present.

The complete type was found only in 3%. Most of them were incomplete and the suspected type. The possible type was 0%, since it was excluded originally.

These are summarized as Table 2.

Table 2. Clinical Features and Subtypes (n=35)

	No. of Pt	%
Manifestations		
Oral ulcer	35	100
Genital ulcer	10	29
Skin lesion	27	77
Uveitis	3	9
Arthropathy	34	97
GI ulcer	2	6
Vascular	2	6
Epididymitis	0	0
CNS lesion	0	0
Subtype		
Complete	1	3
Incomplete	5	14
Suspected	29	83
Possible	0	0

3. Joint manifestations

Joint manifestations appeared in 34 out of 35 patients(97%). Knee, proximal interphalangeal and metacarpophalangeal joints were the main sites. Other involved joints included wrist, elbow, shoulder, ankle, MTP and DIP. Tenderness was prominent in 91% and swelling was noted in 44%. In number of affected joints, monoarticular was 38%, oligoarticular 15% and polyarticular 47%. In most cases, the articular symptom was short-lasting. The duration of arthropathy was less than one week in 59%, one to four weeks in 18%, persisting more than 4 weeks in 18%.

These are summarized as Table 3.

Table 3. Joint Manifestations in Percentages (n=34)

Involved Joint	Knee	91
	PIP	53
	MCP	21
	Wrist	18
	Elbow	15
	Shoulder	12
	Ankle	9
	MTP	3
	DIP	3
	Sign	Tenderness
Swelling		44
Number of Joint	Monoarticular	38
	Oligoarticular	15
	Polyarticular	47
Duration	< 1 week	58.8
	1 to 4 week	17.6
	> 4 week	17.6
	Unclear	5.8

PIP : proximal interphalangeal
MCP : metacarpophalangeal
MTP : metatarsophalangeal
DIP : distal interphalangeal

4. Laboratory and radiologic studies

Basic laboratory tests, including CBC, ESR, complement and immunoglobulin were nonspecific(data not shown) except CRP. CRP was positive in 12 patients and the mean concentration was 2.02 mg/dl (normal < 0.32). It was positive in all complete type and in most of incomplete type. It was also positive in some of suspected type who had very active or advanced manifestations. These are summarized as Table 4.

Table 4. CRP Positivity in Each Subtype

Subtype	No. of Patient	%
Complete(n=1)	1	100
Incomplete(n=5)	4	80
Suspected(n=29)	7	24
Total(n=35)	12	34

RFs were found in 9% and they were all in low titer. ANA was not found at all. HLA B51 was positive in 46%(13/28). Synovial fluid analysis was available in 3 patients. All patients showed inflammatory synovial fluid with polymorphonuclear cells dominant.

Radiologic studies of mainly involved joints were

available in 85% (29/34) of patients. Among these, 90% were normal. Abnormal findings included minimal joint space narrowing and bony osteophytes.

5. Comparison with RA

Thirty five percent(12/34) of patients complained of morning stiffness. It lasted less than 15 minutes in all patients.

Polyarticular presentation was found in 47%. PIP, MCP, wrist, elbow, shoulder, ankle and knee were commonly involved. These were already shown in Table 3.

Thirty one patients visited local medical clinics due to their joint problems. In Table 5, initial diagnoses of the patients by their primary care physicians, later found as Behcet arthritis, were summarized.

Table 5. Initial Diagnosis By Primary Care Physicians (n=31)

Diagnosis	No.of Patient	%
RA, seropositive	2	6.4
RA, seronegative	14	45.2
Arthritis, uncertain	15	48.4

Sixteen patients out of 31 with joint manifestations were carrying a diagnosis of rheumatoid arthritis. None of them were asked by their primary care physicians whether they had recurrent oro-genital ulcers or erythema nodosum-like skin lesions. No definite answer was obtained from their primary care physicians when the patients asked about the relation of skin lesion and the articular symptoms.

DISCUSSION

Behcet disease is a systemic disease classified among vasculitis. The clinical picture is characterized by mucocutaneous and ophthalmologic manifestations. It is seen mostly in countries along the "Silk Road", which include Turkey, Iran, Japan, China and, possibly, Korea.

Behcet disease is diagnosed by a few set of diagnostic criteria, including the Shimizu diagnostic criteria¹⁾ and the International Study Group criteria²⁾. In this study, the Shimizu criteria were used since they were useful in dealing with minor manifestations, including arthritis. The Shimizu criteria are composed of major and minor criteria. Major criteria include recurrent aphthous

ulceration in the mouth, skin lesions (erythema nodosum-like eruptions, subcutaneous thrombophlebitis, hyper-irritability of the skin), eye lesions (recurrent hypopyon iritis or iridocyclitis, chorioretinitis) and genital ulcerations. Minor criteria include arthritic symptoms and signs (arthralgia, swelling, redness), gastrointestinal lesions (appendicitis-like pains, melena, etc.), epididymitis, vascular lesions (occlusion of blood vessels, aneurysms), and central nervous system involvements (brain stem syndrome, meningo-encephalomyelitic syndrome, confusional type). It was proposed by them that if all four of the major symptoms appeared during the clinical course of the disease, the syndrome would be classified as "complete". The "incomplete" type requires three majors or one major symptom and definite ocular involvement. The "suspected" type requires two major symptoms, and the "possible" type requires one major symptom.

There are two comments that should be emphasized. First, in most cases with Behcet disease, various clinical manifestations occur in sequence³⁾. Recurrent oral ulcer is the most common and the earliest symptom, and it is followed by genital and skin lesions. After the skin lesions, arthritis, neurological manifestations and ocular lesions occur which means, although ocular involvement tends to be the most serious problem, it usually does not occur very early in the course of the disease. In other words, although the appearance of uveitis makes the diagnosis of Behcet disease "complete", it does not necessarily mean that we should wait till the patient develops full systemic, lethal manifestations to confirm the diagnosis. Second, among the so-called minors, arthritic manifestation is known as the most common manifestation⁴⁻⁷⁾.

The purpose of this study is to emphasize the clinical significance of Behcet disease, especially when the patients present with arthritic manifestations. In Korea, there were two reports focusing arthritic manifestations in Behcet disease among 150 papers for Behcet disease^{8,9)}. However, one⁸⁾ of them was done in Behcet Disease Specialty Clinic with already known Behcet disease patients, and the other⁹⁾ did not mention in detail how the patients presented to the doctors. The present study was not conducted at Behcet Disease Specialty Clinic, and the author did not intend to collect all Behcet patients from other departments. Most of them just came to the Rheumatology Division with arthralgia or arthritis, one among various early manifestations. That is why the

arthropathy was the most common manifestation, excluding oral ulcer, since it was prerequisite to be enrolled in this study. Since most of them complained of arthritis, the earlier manifestation, the suspected type occupied most of this study group, instead of the clinically more advanced type, such as the incomplete type. The lesser presence of HLA B51 is also explainable by this reason. It was known that there was an association between the presence of HLA B5 and more severe types of Behcet disease¹⁰⁻¹³. Frequency of non-arthritic clinical features were similar to those of previous reports⁴⁻⁷, although the size of the present study group was too small to compare with.

Knee was the most commonly affected joint, as previously reported^{8,9,14}. Sixteen patients with joint manifestations were carrying a diagnosis of RA when they were first enrolled in the present study. Most of them were notified by their primary care physicians as having seronegative RA. It is speculative that they are regarded as satisfying the classification criteria for RA by the articular involvement, morning stiffness¹⁵. It was likely that most doctors were aware of RA and they knew that rheumatoid factor might not be found in some RA patients. To be classified as RA, the joint swelling should be present and persistent, instead of simple tenderness or transient arthritic episode. Morning stiffness should be remarkable, instead of brief discomfort. By careful history taking and thorough physical examination, the author could find out quite easily that they had Behcet arthritis, after all possible rheumatic diseases had been excluded. With full and careful interpretation of all clinical manifestations, it may not be a problem for an experienced physician to differentiate RA with most of Behcet disease. However, for those who do not understand the heterogeneity of rheumatic diseases, Behcet disease may pose a diagnostic dilemma, especially when it presents very similar to RA with polyarticular involvement on PIP, MCP of hands and with equivocal morning stiffness.

Behcet disease was characterized by attacks and remissions¹⁶. It was known that the duration of attacks varied from a few days to a few weeks, and attacks were followed by remissions. Joint manifestations were known usually as non-erosive, even after extended periods of time. In the present study, the duration of each attack was less than 4 weeks in 76%, and this result was similar to the previous report¹. Knee, PIP, MCP, wrist and shoulder were commonly involved, and the arthritic

manifestation was present only for several days in more than half of the patients. In this context, it seemed feasible to say that arthritic manifestations in Behcet disease may present as palindromic rheumatism¹⁷⁻¹⁹. Palindromic rheumatism is characterized by recurrent acute episodes of arthritis. The joints involved in initial attacks in palindromic rheumatism are mostly knee, wrist, MCP, PIP and shoulder¹⁸. Each episode of palindromic rheumatism lasts, not infrequently, for a few weeks¹⁹, and there is no bone and cartilage destruction even after repeated episodes.

CRP was positive in all complete type and most of incomplete type. It was also positive in some of suspected type who had very active or advanced manifestations, such as widespread erythema nodosum-like skin lesion, crippling arthritis (Fig.1-2), gastrointestinal ulceration or vascular aneurysm. It is likely that CRP may be positive in "active" Behcet diseases.



Fig. 1. Twenty-two-year old young man presented with crippling arthritis at left knee joint with markedly elevated CRP. He had arthroscopy at another hospital due to marked swelling and it was unremarkable.

In Korea, even after publication of about 150 papers mentioned above, it seems that Behcet disease is still regarded as a very rare disease to primary care physicians and patients, and especially, the arthritic manifestations in Behcet disease is usually overlooked. It is likely that many doctors do not completely understand the complex nature of Behcet disease, which includes the various clinical spectrum and clinical evolution that was mentioned above in detail. It is speculative that they usually understand Behcet disease as "strict" symptom triad which is composed of oral ulcer, genital ulcer and uveitis. Since they usually think that all manifestations



Fig. 2. Despite marked pain, swelling and limitation of motion, the simple radiologic study was unremarkable.

should appear at the same time, at presentation to them, they will not diagnose a patient as Behcet disease if the patient has only one or two manifestations. Patients with oro-genital ulcers may not seek help since the clinical manifestation is sometimes tolerable or relieved by topical agents. Otherwise, they may feel uncomfortable in visiting a doctor's office with genital problems which are not very urgent. Various skin lesions, including erythema nodosum-like eruptions, subcutaneous thrombophlebitis and hyper-irritability of the skin, manifest so diverse and are mostly subclinical. From these contexts, arthralgia or arthritis can be the first presenting problem in many Behcet disease patients.

The present study had a few limitations. The size of the sample was too small and the duration of follow-up was too short to discuss the entire clinical progression. Most patients were the incomplete or suspected type, instead of the complete type, since the author focused on early presenting manifestations and early detection. By the way, recently, there was a report focusing heel pain in Behcet disease patients which suggested that arthropathy in Behcet disease might be regarded as another entity of seronegative spondyloarthropathy²⁰⁾. In the present study, heel pain was present in one patient.

The present study was focused only on articular manifestations and future study, including the enthesopathy, seems to be required.

CONCLUSION

In Behcet disease, various manifestations can be found. The arthritic manifestation seems quite common. It may present as seronegative rheumatoid arthritis. Otherwise, it may present as palindromic rheumatism. Much more attention to this disease and a nationwide survey in Korea seem to be required for better understanding, early detection and appropriate treatment.

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