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The Comparison Between Behçet's Disease and Spondyloarthritides: Does Behçet's Disease Belong to the Spondyloarthropathy Complex?

This study was to clarify whether Behçet's disease (BD) could be classified into the spondyloarthropathy (SpA) complex. It was undertaken on 58 patients with BD (BD group), 56 patients with SpA (SpA group), and 3 patients who concurrently satisfied the criteria for BD and SpA (BDSpA group). The clinical parameters and known susceptible HLA antigens were compared between BD group and SpA group. In addition, 3 patients in BDSpA group were reviewed. The prevalence of definitive sacroiliitis (SI) in BD group and SpA group was 46.4% and 5.2%, respectively. However, none had a definitive SI in healthy controls. Enthesitis was observed in 3.4% of BD group and in 50% of SpA group. The patterns of eye involvement were different between these two groups. HLA-B27 was negative in all 49 patients of BD group, whereas it was positive in 67.9% of SpA group. The prevalence of HLA-B51 was 51.7% in BD group, and that in SpA group was 21.4%. One patient in BDSpA group was considered to have concurrent BD and ankylosing spondylitis (AS). Another patient was closer to AS, and the third to BD. Conclusively, it seems that BD could not be classified into the SpA complex.

Key Words : *Behçet's Syndrome; Spondyloarthropathies*

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INTRODUCTION

Although Moll et al. suggested that Behçet's disease (BD) could be included in the spondyloarthropathy (SpA) complex in 1974 (1), it is still debatable whether BD is one of this disease complex. To date, the following evidences may support this hypothesis. First, some investigators have reported an increased prevalence of sacroiliitis (SI) in patients with BD. Second, several cases that simultaneously satisfied the classification criteria for BD and ankylosing spondylitis (AS) or SpA have been reported. Third, there is a clinical overlap between BD and some diseases of the SpA complex such as inflammatory bowel disease and Reiter's syndrome.

The frequency of SI and AS in patients with BD has been variably described according to investigators and countries studied. Yazici et al. claimed that the high prevalence of SI in BD might be due to a high observer variation in interpreting the film of anteroposterior (AP) view of the pelvis, or the studies which used no controls or were not performed in a blinded pattern (2). In addition, Olivieri et al. pointed out that the different origin of the series of BD and the different diagnostic criteria used for diagnosing BD before the International Study Group (ISG) criteria might be another causes of these discrepancies (3). On the other hand, they described 4 patients with SI among 20 patients with BD by using computed tomography (4).

Up to date, the studies for this issue have been mainly limited to whether the prevalence of SI or AS is greater in patients with BD. Therefore, we performed a study to compare the characteristic clinical features and known susceptible HLA antigens such as HLA-B27 and HLA-B51 in patients with BD or SpA, to clarify whether BD could be classified into the SpA complex. In addition, patients who concurrently satisfied the classification criteria of BD and SpA were reviewed.

MATERIALS AND METHODS

This study was prospectively undertaken on 58 patients with BD (20 males and 38 females) (BD group) who satisfied the ISG criteria (5), 56 patients with SpA (39 males and 17 females) (SpA group) who fulfilled the criteria by the European Spondyloarthropathy Study Group (ESSG) (6), 3 male patients who concurrently satisfied the criteria of ISG and ESSG (BDSpA group). The patients in these three disease groups have been followed up from March 1999 to March 2001. The mean follow-up periods (±SD) of BD group and SpA group were 14.6 months (±8.9) and 15.3 months (±

8.3), respectively. The SpA group consisted of 28 patients with AS, 22 undifferentiated SpA, 3 psoriatic arthritis, 2 reactive arthritis, and 1 enteropathic arthritis. The healthy controls were composed of 56 healthy individuals (21 males and 35 females) who had visited for a medical checkup. The mean ages (±SD) of patients in BD group and SpA group were 41.6 yr (±10.2) and 31.8 yr (±10.2), respectively. The mean age of the healthy controls was 42.7 yr (±10.0).

AP pelvis radiographs were obtained from all individuals after informed consent. Two radiologists and one rheumatologist read the radiographs in a random manner by the grading system of SI according to the New York criteria (7) without clinical information. It was considered to have SI when 2 investigators interpreted as over grade 2 in each individual. In addition, patients were considered to have a definitive SI when 2 investigators interpreted as over grade 3 or all 3 investigators read as over grade 2.

Enthesitis was documented as past or present pain or tenderness on examination of the insertion of the Achilles tendon or plantar fascia, present pain and tenderness at the iliac crests, greater trochanters, ischial tuberosities, and tibial tuberosities (6, 8). All individuals in three disease groups were examined and educated for an ocular manifestation by the same ophthalmologist at the initial visit and whenever the ocular manifestations occurred.

The test for HLA-B27 antigen was performed using microlymphocytotoxicity method in 49 patients of BD group, in all patients of SpA group or BDSpA group. HLA-B51 was tested by the two-step polymerase chain reaction with sequence-specific primers method in all patients (9, 10). Statistical analysis was done by Fisher's exact test. The *p*-values less than 0.05 were considered to be statistically significant. In addition, three patients in BDSpA group were reviewed.

RESULTS

SI was found in 58.9% of SpA group, in 10.3% of BD group, and in 3.6% of healthy controls. The prevalence of SI in BD group was significantly lower than that in SpA group ($p<0.001$), and although it was slightly higher than in healthy controls, there was no statistically significant difference between these two groups ($p=0.272$). In addition, the definitive SI was observed in 46.4% of SpA group and in 5.2% of BD group. However, none had the definitive SI in healthy controls, and there was no statistically significant difference in frequencies of definitive SI between BD group and healthy controls (Table 1).

The enthesitis was found in 2 patients of BD group (3.4%) and in 28 patients of SpA group (50%) ($p<0.001$). The ocular involvement was found in 12 patients (20.7%) of BD group in the following patterns: 7 patients with anterior and posterior uveitis (12.1%), 2 patients with posterior uveitis and retinal vasculitis (3.4%), 2 patients with anterior uveitis (3.4%), and 1 patient with scleritis (1.7%). However, all ten patients with the ocular involvement in SpA group (17.9%) had anterior uveitis.

HLA-B27 was negative in all 49 patients of BD group, and it was positive in 38 patients of SpA group (67.9%). The prevalence of HLA-B51 in BD group was 51.7% and that in SpA group was 21.4% ($p=0.001$).

Patients in BDSpA group

The clinical features of three patients in BDSpA group are summarized in Table 2.

Patient 1

A 28-yr-old man presented with a painful swelling of the right knee. This patient was previously described (11). Briefly, he had a past history of recurrent oral ulcerations, 2 episodes of painful scrotal ulcerations, pain on the right heel, and the lower back pain that was worsened in the early morning and improved with activity. Physical examination revealed multiple aphthous ulcers on the buccal mucosa, papulopustular lesions on the anterior chest, scrotal ulcer, and inflammatory synovitis on the right knee. The modified Schober test was 15 cm and the chest expansion was 5 cm. The pathergy reaction was negative. Both HLA-B27 and B51 antigens were positive. Bilateral SI (right: grade 4, left: grade 3) was noted on plain pelvis radiograph and magnetic resonance imaging (MRI) (Fig. 1). While being treated, recurrent acute iritis with hypopyon, posterior uveitis, and papillitis in both eyes

Table 1. The prevalence of sacroiliitis in BD group, SpA group and in healthy controls

	No. of patients	No. of patients with sacroiliitis (%)	No. of patients with definitive sacroiliitis (%)
SPA	56	33 (58.9)	26 (46.4)
BD	58	6 (10.3)*	3 (5.2)†
Controls	56	2 (3.6)‡	0§

BD, Behçet's disease; SpA, spondyloarthropathy.
p-value between SpA group and BD group: *, <0.001; †, <0.001.
p-value between BD group and healthy controls: ‡, 0.272; §, 0.244.

Table 2. The clinical features of patients in BDSpA group

	Patient 1	Patient 2	Patient 3
Age (yr)/sex	28/male	31/male	55/male
Orogenital ulceration	+	+	+
Skin lesion	+	+	–
Pathergy reaction	–	–	+
Ocular lesion	+*	+†	–
Inflammatory spinal pain	+	+	–
Sacroiliitis	+	+	–
Peripheral arthritis	+	–	+
Enthesitis	+	+	+
HLA-B51/B27	+/+	+/+	–/+

*, Recurrent posterior uveitis; †, Recurrent anterior uveitis.

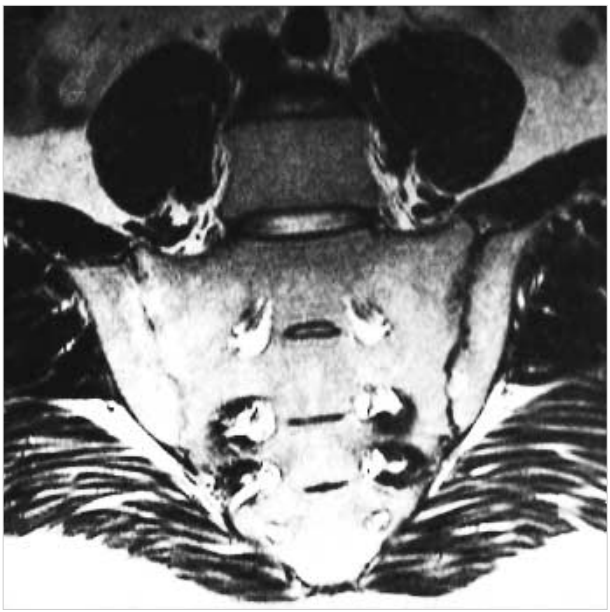

Fig. 1. T2-weighted magnetic resonance imaging shows an increased signal intensity of subchondral marrow, and an obliteration of joint space in both sacroiliac joints (right>left).

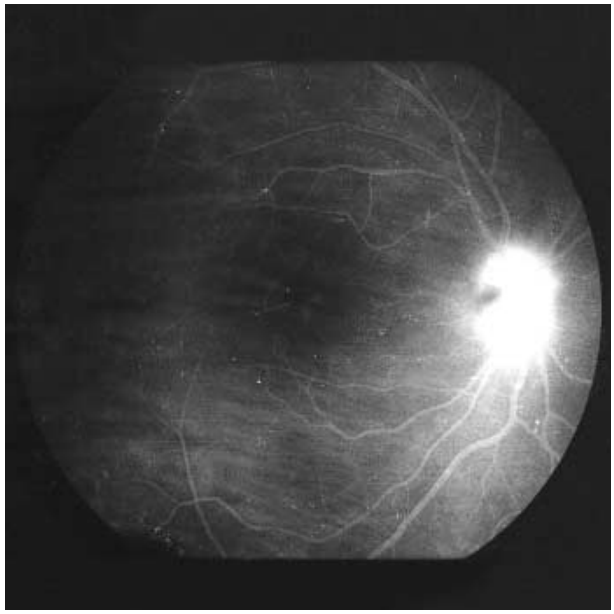

Fig. 2. Fluorescein angiogram of the right eye reveals a prominent leaking of optic disc and diffuse hyperfluorescence due to posterior vitritis.

were developed (Fig. 2). This case fulfilled the ISG criteria and the modified New York criteria for AS (7).

Patient 2

A 31-yr-old man was referred to our clinic for recurrent anterior uveitis and recurrent oral ulcerations from the ophthalmologic department. His past history included recurrent oral ulcerations, 2 episodes of ulcerations on the glans penis, three events of right anterior uveitis, pain on the left heel, left buttock, and lower back. The lower back pain was more prominent in the early morning and was relieved with exercise. He denied any history of conjunctivitis, urethritis, psoriasis, or a severe bout of diarrhea. Physical examination revealed aphthous ulcerations on the tongue and multiple papulopustular lesions on the back. The modified Schober test was 14.5 cm and the chest expansion was 3 cm. The pathergy reaction was negative. HLA-B27 and HLA-B51 were positive. The plain radiograph and MRI of pelvis revealed bilateral grade 2 SI. During the follow-up, one episode of small ulceration on the glans penis occurred, which was not painful and healed without scarring lesion. He concurrently satisfied the ISG criteria and the modified New York criteria.

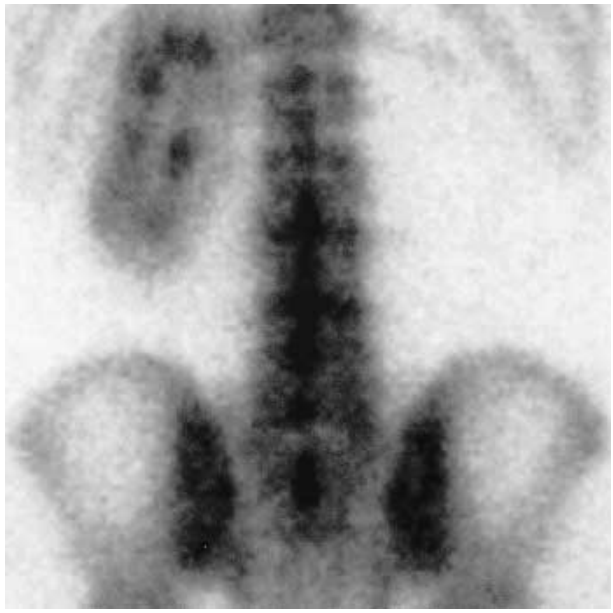

Fig. 3. Increased uptake on the spinous processes of lower lumbar spines is seen on the posterior image of bone scan.

Patient 3

A 55-yr-old man presented with pain and stiffness of hip girdle and lower back, diarrhea, and pain on the right lower abdomen. His medical history disclosed recurrent oral ulcerations and 2 episodes of scrotal ulcerations. Physical examination showed tenderness of the right lower abdomen, inflammatory synovitis of the right knee, and two scarring lesions on the scrotum. Pain was elicited on pressure over the iliac crests, right heel, and lower lumbar spinous processes. The pathergy reaction was positive. HLA-B51 antigen was negative, and HLA-B27 antigen was positive. There were no abnormal findings in the plain pelvic radiograph. Bone scan and single photon emission computed tomography (SPECT) showed an arthritic change on the right knee as well as an

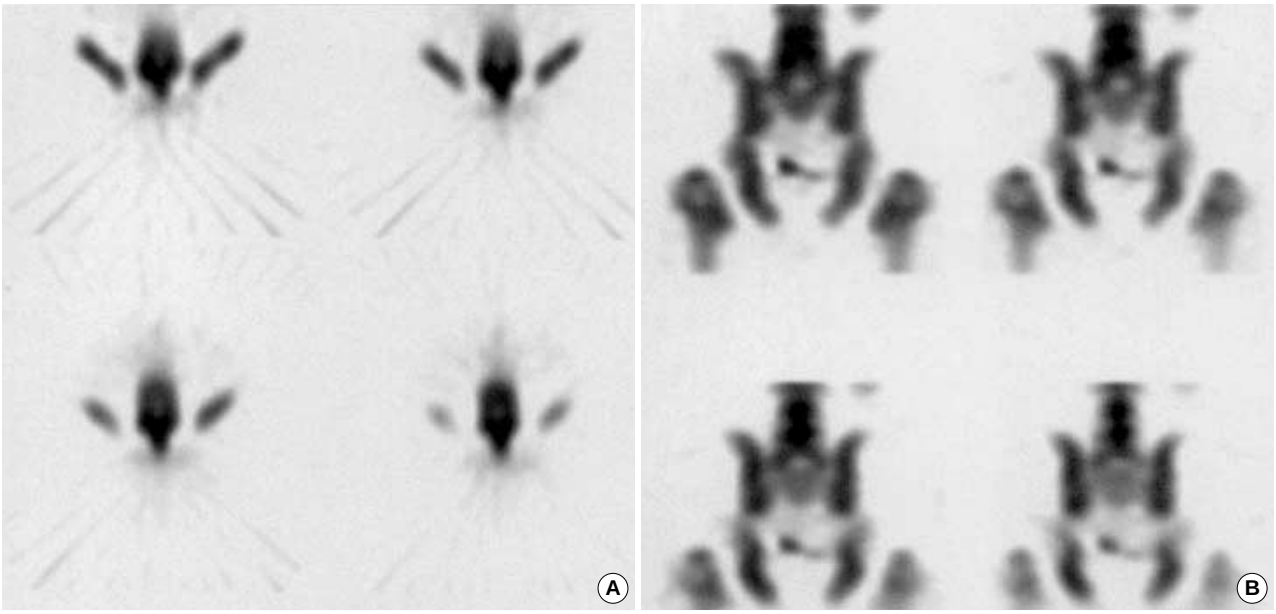

Fig. 4. Transverse (A) and coronal SPECT (B) slices through lower lumbar spines and pelvis show intense tracer uptake on the both laminae and spinous processes of L4 and L5.

increased activity on the both laminae and spinous processes around the 4th and 5th lumbar vertebrae consistent with enthesitis (Fig. 3 and Fig. 4). However, the sacroiliac joints were intact on the bone SPECT. Colonoscopy revealed multiple ulcerations on the terminal ileum and ascending colon. During the follow-up, he underwent a segmental resection of the small intestine due to bleeding and perforation on the ulceration of the terminal ileum. This case fulfilled the ISG criteria and the ESSG criteria.

DISCUSSION

Moll et al. suggested that BD could be one of the SpA complex on the basis of the following criteria: negative tests for rheumatoid factor, absence of subcutaneous ("rheumatoid") nodules, inflammatory peripheral arthritis, radiological SI with or without classical AS, evidence of clinical overlap between members of the group, and tendency to familial aggregation (1). On the other hand, the clinical spectrum of SpA has been recently expanded and has included the clinical disorders without any involvement of the axial skeleton. In addition to AS, a prototype of SpA, reactive arthritis (including Reiter's syndrome), arthritis associated with chronic inflammatory bowel disease, psoriatic arthritis, undifferentiated SpA, and a subgroup of juvenile chronic arthritis have been comprised in the SpA complex (1, 6, 12). However, the inclusion of BD into this disease entity is still debatable.

Some investigators have reported a high prevalence of AS or SI in patients with BD (13-15). In addition, several patients with coexisting AS and BD have been described in the literature (11, 16-19). However, other authors have found that the prevalence of AS or SI in BD has not been different from that in the general population (20-24). Although Dilsen et al. reported the highest level of 33 (10%) patients with AS and 112 (34%) with SI among 334 Turkish patients with BD (13), other authors found no evidence of an increased frequency of SI in patients with BD and described only one patient with definitive AS among 114 patients with BD in the same population (20).

Yazici et al. pointed out that the inter-observer variation might be a major cause of discrepancies in interpreting AP pelvis radiographs for SI (2). On the other hand, Olivieri et al. suggested that computed tomography could reduce errors in the radiological evaluation of the sacroiliac joint (4). There could be no difficulty in interpreting SI in patients with moderate or advanced SI. Major problem existed in minimal SI or lower grades of SI (2, 21). The current study showed that the frequency of SI in BD group was slightly increased without statistical significance when compared to healthy controls. Because of the possibility of observer's variation in reading plain pelvis radiographs, we took the definitive SI into account in our study groups. Definitive SI was not encountered in healthy controls, and it was found in 3 of BD group (2 patients with unilateral SI and one patient with bilateral SI).

Besides the patients with coexisting BD and AS, cases that concurrently met the criteria for BD and SPA without AS have been reported (25-27). Of interest, a patient with BD and undifferentiated SpA who had evolved into psoriatic arthritis after 3 yr of the disease was described (25). A patient affected by BD without SI or AS but with peripheral enthe-

sitis typical of SpA was reported (27), who resembles our patient 3 with the exception of enthesitis involving the structures around the axial skeleton. BD patients with enthesitis involving the axial skeleton have not been described to our knowledge. The enthesitis associated with BD has rarely been found in the literature (14, 23). Only two patients in our BD group had enthesitis, in whom one patient had right Achilles tendinitis and the other had enthesitis on the right tibial tuberosity.

The course of eye involvement is known to be different between BD and AS. The HLA-B27-associated uveitis in SpA mostly involves the anterior uveal tract and relatively follows a benign course. However, the uveitis in BD usually involves both anterior and posterior uveal tracts, and causes the loss of sight in 25% of patients (28-30). As shown previously, the patterns of eye involvement in BD group and SpA group of our study were different. The eye involvement in BD group was mostly on the posterior uveal tract, and that in SpA group was totally on the anterior uveal tract. We experienced a 46-yr-old female with BD who developed a nodular scleritis (31).

The diseases in SpA complex share several common features, of which one of the most salient is the association with HLA-B27 antigen. So far, there have been conflicting results for the prevalence of HLA-B27 in patients with BD. Chamberlain found that the overall frequency of HLA-B27 in BD patients was significantly increased, and that the level was similar to that found in psoriasis (24). Lehner et al. described an increased incidence of HLA-B27 in BD patients with arthritis (32). On the other hand, others reported no association with this antigen in BD (14). The prevalence of HLA-B27 in the general population has shown a considerable geographic variation, and that in healthy Koreans in one study was 5.7% (33). In this study, we could not find any BD patient with HLA-B27 antigen with an exception of patients who concurrently fulfilled the criteria for AS or SpA. HLA-B51 antigen has been well-known genetic factor associated with BD. The prevalence of this antigen in BD appears to be higher in countries adjacent to the ancient silk road including Korea (10, 34, 35). In the present series, the frequency of HLA-B51 in BD group was significantly higher than that in SpA group. Because BD seems to be associated with HLA-B51 rather than HLA-B27, this finding strongly argues against the hypothesis that BD could be a part of SpA complex.

Patient 1 had clinical manifestations consistent with BD and AS. Both the HLA-B51 and B27 antigens were reported to be more frequent in patients with coexisting BD and AS (13), and in line with this, Patient 1 had both HLA-B51 and B27 antigens. This patient was considered to have actually concurrent BD and AS. Patient 2 was initially diagnosed as BD. However, due to the presence of bilateral SI, the patient was reevaluated. He had a past history consistent with inflammatory spinal pain and enthesitis. His recurrent uveitis mainly involved the anterior uveal tract. The genital ulceration that developed during the follow-up was a painless small ulceration on the glans penis, and healed without scar formation, which was clinically different from the genital ulcerations of BD. We thought the clinical features of Patient 2 were closer to AS, although he had both HLA-B51 and B27. Patient 3 had several manifestations typical of BD, except enthesitis, and was considered to have rather BD than SpA. To date, there have been no specific tools to diagnose the BD or SpA, and the diagnosis mainly depends on the clinical features and an experienced physician's judgement.

In summary, there was no patient with HLA-B27 in BD group. SI or enthesitis was found in a minor portion of patients in BD group. In addition, the patterns of eye involvement in BD group were different from those in SpA group. We share the view with some authors that BD is not a part of SpA complex (3, 36). However, it still remains unclear why there have been many patients with coexisting BD and AS or SpA, including our cases. On the other hand, in the cases that have a SI among patients with BD, more thorough reevaluation will be necessary.

REFERENCES

1. Moll JMH, Haslock I, Macrae IF, Wright V. *Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behçet's syndrome. Medicine (Baltimore) 1974; 53: 343-64.*
2. Yazici H, Turunc M, Özdogan H, Yurdakul S, Akinci A, Barnes CG. *Observer variation in grading sacroiliac radiographs might be a cause of 'sacroiliitis' reported in certain disease states. Ann Rheum Dis 1987; 46: 139-45.*
3. Olivieri I, Salvarani C, Cantini F. *Is Behçet's disease part of the spondyloarthritis complex? J Rheumatol 1997; 24: 1870-2.*
4. Olivieri I, Gemignani G, Camerini E, Semeria R, Pasero G. *Computed tomography of the sacroiliac joints in four patients with Behçet's syndrome: confirmation of sacroiliitis. Br J Rheumatol 1990; 29: 264-7.*
5. International Study Group for Behçet's disease. *Criteria for diagnosis of Behçet's disease. Lancet 1990; 335: 1078-80.*
6. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, Cats A, Dijkmans B, Olivieri I, Pasero G, Veys E, Zeidler H. *The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991; 34: 1218-27.*
7. Van der Linden S, Valkenburg HA, Cats A. *Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984; 27: 361-8.*
8. Mander M, Simpson JM, McLellan A, Walker D, Goodacre JA, Dick WC. *Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. Ann Rheum Dis 1987; 46: 197-202.*
9. Hein J, Böttcher K, Grundmann R, Kirchner H, Bein G. *Low resolution DNA typing of the HLA-B5 cross-reactive group by nested PCR-SSP. Tissue Antigens 1995; 45: 27-35.*
10. Chang HK, Kim JU, Cheon KS, Chung HR, Lee KW, Lee IH. *HLA-*

B51 and its allelic types in association with Behçet's disease and recurrent aphthous stomatitis in Korea. Clin Exp Rheumatol 2001; 19: S31-5.

11. Chang HK, Cho EH, Kim JU, Herr H. *A case of coexisting Behçet's disease and ankylosing spondylitis. Korean J Intern Med 2000; 15: 93-5.*
12. Khan MA, van der Linden SM. *A wider spectrum of spondyloarthropathies. Semin Arthritis Rheum 1990; 20: 107-13.*
13. Dilsen N, Konice M, Aral O. *Why Behçet's disease should be accepted as a seronegative arthritis. In: Lehner T, Barns CG, editors, Recent Advances in Behçet's Disease. London: Royal Society of Medicine Services, 1986: 281-4.*
14. Caporn N, Higgs ER, Dieppe PA, Watt I. *Arthritis in Behçet's syndrome. Br J Radiol 1983; 56: 87-91.*
15. Olivieri I, Gemignani G, Pecori F, Semeria R, Pasero G. *Coexisting ankylosing spondylitis and Behçet's syndrome: a report of six cases. In: O'Duffy JD, Kokmen E, editors, Behçet's Disease: Basic and Clinical Aspects. New York: Marcel Dekker, 1991: 247-52.*
16. Tosun M, Uslu T, Ibrahim Imamoglu H, Bahadir S, Erdolu S, Guler M. *Coexisting ankylosing spondylitis and Behçet's disease. Clin Rheumatol 1996; 15: 619-20.*
17. Olivieri I, Gemignani G, Busoni F, Pecori F, Camerini E, Trippi D Pasero G. *Ankylosing spondylitis with predominant involvement of the cervical spine in a woman with Behçet's syndrome. Ann Rheum dis 1988; 47: 780-3.*
18. Beiran I, Scharf J, Dori D, Miller B. *A change in ocular involvement in a patient suffering from ankylosing spondylitis and Behçet's disease. Eur J Ophthalmol 1995; 5: 192-4.*
19. Borman P, Bodur H, Ak G, Bostan EE, Barca N. *The coexistence of Behçet's disease and ankylosing spondylitis. Rheumatol Int 2000; 19: 195-8.*
20. Yazici H, Tuzlaci M, Yurdakul S. *A controlled survey of sacroiliitis in Behçet's disease. Ann Rheum Dis 1981; 40: 558-9.*
21. Chamberlain MA, Robertson RJ. *A controlled study of sacroiliitis in Behçet's disease. Br J Rheumatol 1993; 32: 693-8.*
22. Shimizu T, Ehrlich GE, Inaba G, Hayashi K. *Behçet's disease (Behçet's syndrome). Semin Arthritis Rheum 1979; 8: 223-60.*
23. Yurdakul S, Yazici H, Tuzun Y, Pazarli H, Yalcin B, Altac M, Ozyazgan Y, Tuzuner N, Muftuoglu A. *The arthritis of Behçet's disease: a prospective study. Ann Rheum dis 1983; 42: 505-15.*
24. Chamberlain MA. *Behçet's syndrome in 32 patients in Yorkshire. Ann Rheum Dis 1977; 36: 491-9.*
25. Padula A, Ciancio G, Cantini F, Barozzi L, Scarano E, Niccoli L, Olivieri I. *Coexisting Behçet's syndrome and spondyloarthritis. Clin Rheumatol 1999; 18: 499-500.*
26. Olivieri I, Cantini F, Napoli V, Braccini G, Padula A, Pasero G. *Seronegative spondylarthropathy without spine involvement in Behçet's syndrome. Clin Rheumatol 1993; 12: 396-400.*
27. Olivieri I, Gemignani G, Braccini G, Pasero G. *Behçet's syndrome and spondyloarthritis. Br J Rheumatol 1990; 29: 409-10.*
28. Van der Linden S, van der Heijde D. *Ankylosing spondylitis. In: Ruddy S, Harris ED Jr, Sledge CB, editors, Kelly's Textbook of Rheumatology. Philadelphia: W.B. Saunders, 2001; 1039-53.*
29. Kaklamani VG, Vaiopoulos G, Kaklamanis PG. *Behçet's disease. Semin Arthritis Rheum 1998; 27: 197-217.*
30. Hazleman BL. *Rheumatic disorders of the eye and the various structures involved. Br J Rheumatol 1996; 35: 258-68.*
31. Chang HK, Cho EH. *A case of nodular scleritis in association with Behçet's disease. Korean J Intern Med 2001; 16: 47-9.*
32. Lehner T, Batchelor JR. *Classification and an immunogenetic basis of Behçet's syndrome. In: Lehner T, Barns CG, editors, Behçet's Syndrome. New York: Academic Press, 1979; 13-32.*
33. Jeon HY, Youn JE, Lee YS, Park MH. *Association between psoriasis and HLA-antigen. Korean J Dermatol 1990; 28: 159-86.*
34. Verity DH, Marr JE, Ohno S, Wallace GR, Stanford MR. *Behçet's disease, the silk road and HLA-B51: historical and geographical perspectives. Tissue Antigens 1999; 54: 213-20.*
35. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Goto K, Nakamura S, Bahram S, Ohno S, Inoko H. *Association analysis between the MIC-A and HLA-B alleles in Japanese patients with Behçet's disease. Arthritis Rheum 1999; 42: 1961-6.*
36. Yazici H, Yurdakul S, Hamuryudan V. *Behçet's Syndrome. In: Klippel JH, Dieppe PA, editors, Rheumatology. London: Mosby, 1998: 7.26.1-6.*