Coexistence of Behcet's Disease and Ankylosing Spondylitis: Case Report

Behçet Hastalığı ve Ankilozan Spondilit Birlikteliği: Olgu Sunumu

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ABSTRACT

Behçet's disease (BD) and HLA-B27 positive ankylosing spondylitis (AS) coexistence is a rare occurrence with only few reports in the literature. We reported here a patient with coexisting BD and AS demonstrating both HLA-B27 and HLA-B51 positivity.

Keywords: Behçet's disease, ankylosing spondylitis, HLA-B27 and HLA-B51 positivity

ÖZET

Behçet hastalığı (BH) ve HLA-B27 pozitif ankilozan spondilit (AS) birlikteliği literatürde sadece birkaç raporla sınırlı, nadir görülen bir durumdur. Biz burada hem HLA-B27 hem de HLA-B51 pozitifliği gösteren BH ve AS birlikteliği olan bir olgu sunduk.

Anahtar sözcükler: Behçet hastalığı, ankilozan spondilit,HLA-B27 ve HLA-B51 pozitifliği

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Introduction

Behçet's disease (BD) is an inflammatory disease characterized with recurrent oral and genital aphthous ulcerations, uveitis, and skin lesions (1). BD arthritis is usually mono or oligoarticular. Oligoarthritis in the small or larger joints is seen in nearly 40 % of BD patients. In BD, joint involvement, particularly of the large joints of the lower extremity, is common. The most commonly involved joint is the knee, followed by the joints of ankle, elbow, and wrist (1,2). In addition, various rates of incidences for sacroiliitis and spondylitis have also been reported by different studies from different countries (3-7).

Ankylosing spondylitis (AS) is a prototype of seronegative spondiloarthroptahies (SpA) characterized by the involment of axial skeleton, predominatly the sacroiliac joints, resulting in a restriction of the spine and producing progressive disability (8,9). It is genetically significantly associated with HLA-B27. It is the most common type among seronegative SpAs and defined as a typical disease centering the group of psoriatic arthritis, reactive arthritis, enteropathic arthritis, inflammatory bowel disease associated arthritis, and undifferentiated spondyloarthropathy which are demonstrated common demographic, clinical, and genetic traits. In 20-30% of AS patients, the disease progresses with peripheral joint involvement, mostly involving the joints of the hip, knee, and shoulder (10).

BD has been classified as SpA by some rheumatologists because of erosive sacroiliitis and inflammatory spinal pain. Although a high incidence of sacroiliitis has been reported in BD patients, the absence of a familial

relationship with other SpAs in seronegative SpA group and higher association with HLA-B51 than with HLA-B27 suggest that BD should not be classified in seronegative SpAs (11,12). Co-existence of BD and HLA-B27 positive AS is a very rare occasion, with very few reports in the literature (10,12-17).

This report has presented an HLA-B51 and HLA-B27 positive patient with coexisting BD and AS based on clinical and laboratory findings.

Case Report

A 46-year-old patient was admitted to our outpatient clinic with the complaints of low back pain of 6 months that increased at rest, particularly in the mornings, and decreased with activity and the complaints of pain in the right ankle without any inflammatory sign including swelling. The history of the patient revealed recurrent oral aphthous ulcerations (5-6 times a year) for the last 10 years, 4-5 skin lesions on the anterior surface of the tibia for the last 1-2 years, multiple previous anterior uveitis attacks, and positive pathergy test result. The patient was diagnosed with BD according to the criteria of International Study Group (ISG) (18). After the diagnosis, the patient had been receiving 1.5 mg/day colchicine. The familial history of the patient showed that his uncle had been followed with diagnosis of AS for 20 years. On physical examination, the lomber spine range of motion were slightyl painful and limited just at the end of movement. Bilateral sacroiliac compression tests were positive. In the examinations of the peripheral joints, the right ankle of the patient was swollen and sensitive upon palpation. The other peripheral joint examianations were normal. In the laboratory investigations, total blood count, routine biochemical tests, immunglubolin and complement levels were within normal range. Erythrocyte sedimentation rate was 22 mm/hour; C-reactive protein: 1.43mg/dL (normal range: 0-0.8 mg/dl); rheumatoid factor was negative; and HLA-B27 and HLA-B51 were positive. Anteroposterior plain radiograph of the pelvis revealed irregular contour and erosions of the bones comprising both sacroiliac joints, narrowing of the left sacroiliac joint space, and syndesmophyte in the thoracolumbar region (Figure 1a). In anteroposterior plain radiograph of right foot and ankle, an appearance compatible with the soft tissue swelling was observed in the talo-calcaneal area, however, there were no erosions or enthesitis. Magnetic resonance imaging (MRI) of sacroiliac joints showed irregular contours and erosions of the bony structures forming the sacroiliac joint and narrowing of the left sacroiliac joint space (bilateral stage 3 sacroiliitis) (Figure 1b).

The patient fulfilled the diagnostic criteria for AS according to the modified New York criteria. Considering his follow-up since 2005 with the diagnosis of BD, presence of inflammatory spinal pain, and detection of stage 3 bilateral sacroiliitis on MRI of the sacroiliac joints, HLA-B51 and HLA-B27 positivity, the diagnosis was thougth as BD and AS coexistence in the light of the clinical, laboratory and imaging findings and thus, 2 gr/day of sulphasalasine was added to the treatment regimen.

Discussion

BD and HLA-B27 positive AS coexistence is a rare occurrence with only few reports in the literature (10,12-17). In a study conducted in Korea, Chang et al have reported three cases of coexisting BD and SpA (12). The clinical characteristics of these three patients and our patient have been presented in Table 1.

Table 1. The characteristic features of our case and previous concomitant AS and BD cases reported by Chang et al.

		Concomitant AS and BD cases reported by Chang et al.		
	Our patient*	**Patient 1***	**Patient 2***	**Patient 3****
Age (yr)/sex	46/male	28/male	31/male	55/male
Orogenital ulceration	+	+	+	-
Skin lesion	+	+	+	+
Pathergy reaction	+	-	-	-
Ocular lesion***	+	+	+	-
HLA-B27	+	+	+	+

***** The findings of the patients meet the criteria of ISG and modified New York criteria.
** The findings of the patient meet the criteria of ISG and European Spondyloarthropathy Study Group
*** Our patient and patient 2 have anterior uveitis, while patient 1 has posterior uveitis , patient 3 does not have any eye involvement.

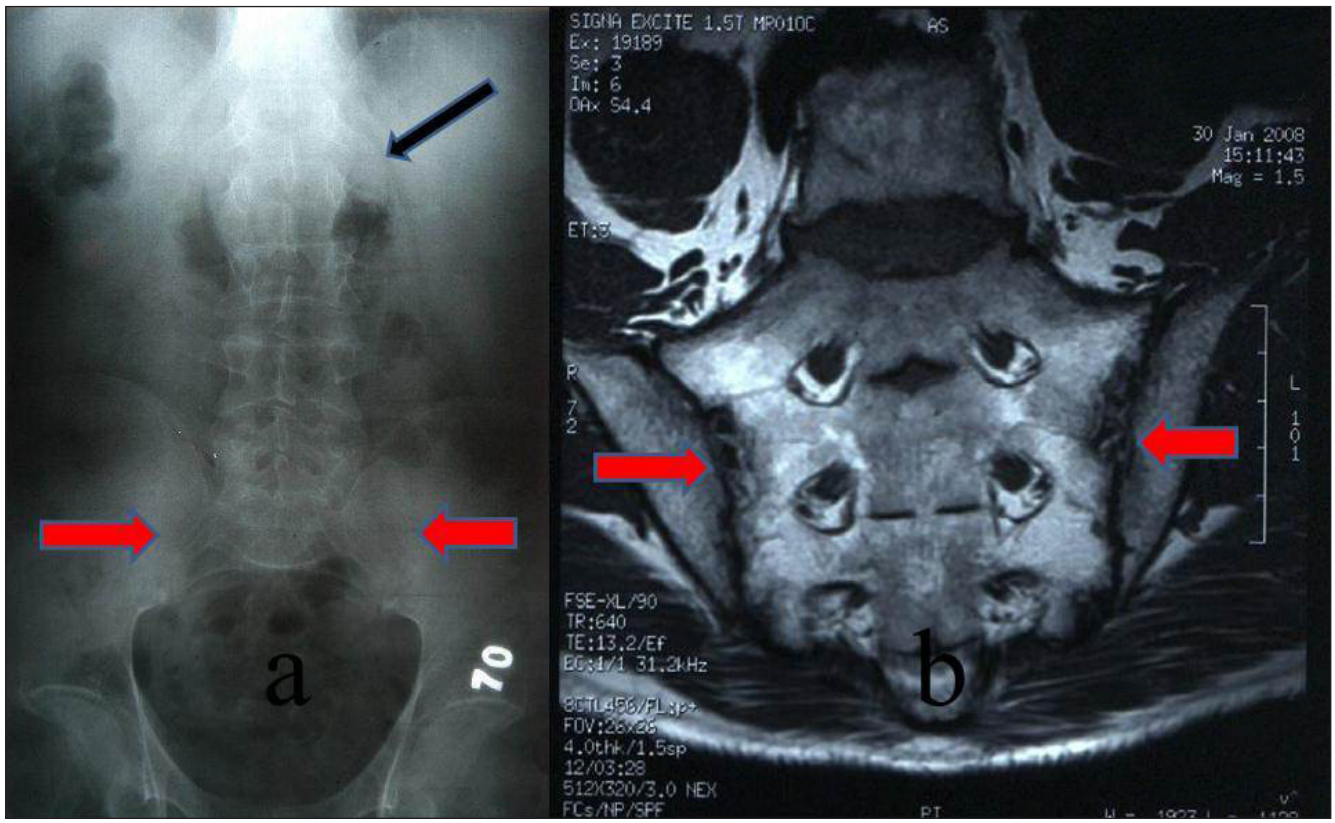


Figure 1. a: Anteroposterior plain radiograph of the pelvis revealed stage 3 bilateral sacroiliitis including irregular contour and erosions of the bones comprising both sacroiliac joints (red arrows), narrowing of the left sacroiliac joint space and syndesmophyte (black arrow) in the thoracolumbar part of spine.
b: Magnetic resonance imaging (MRI) of sacroiliac joints showed stage 3 bilateral sacroiliitis and irregular contours, erosions and narrowing of the sacroiliac joint was prominent at the left side than right side (red arrows).

Moll et al have proposed that BD can be classified in SpAs, which has been held in controversy (11). However, literature reveals some evidence in support of this hypothesis. Some earlier reports have shown increased prevalence of sacroiliitis and inflammatory spinal pain in BD (12-14). Another support is the presence of cases meeting the criteria of both BD and AS or SpA classification. Still another support is the presence of clinically overlapping syndromes such as BD, inflammatory bowel disease, and Reiter syndrome, which are classified in SpAs.

There are conflicting reports on the incidence of AS and sacroiliitis coexistence in BD. Evaluation of the patients according to various criteria and limited number of patients in the series presented lead to difficulties in reaching a common consensus. Dilşen et al have reported an incidence rate of 10% for AS in BD (4), while Yazici et al have detected only one AS patient in a series of 184 patients with BD (3). Despite reports of varying incidence rates of sacroiliitis (5.2-34%) in BD, according to some studies, the incidence of sacroiliitis in BD does not increase compared to that in normal population (5,6,19). The inconsistency between the results of relevant studies has been attributed to the various interpretations of anterioposterior pelvis graphs. Although no difficulties have been encountered in the interpretation of moderate and severe sacroiliitis, the main difficulty has been experienced in interpreting low grade or early stage sacroiliitis (20). Thus, the use of advanced imaging modalities in determining low grade or early stage sacroiliitis has been advocated (7).

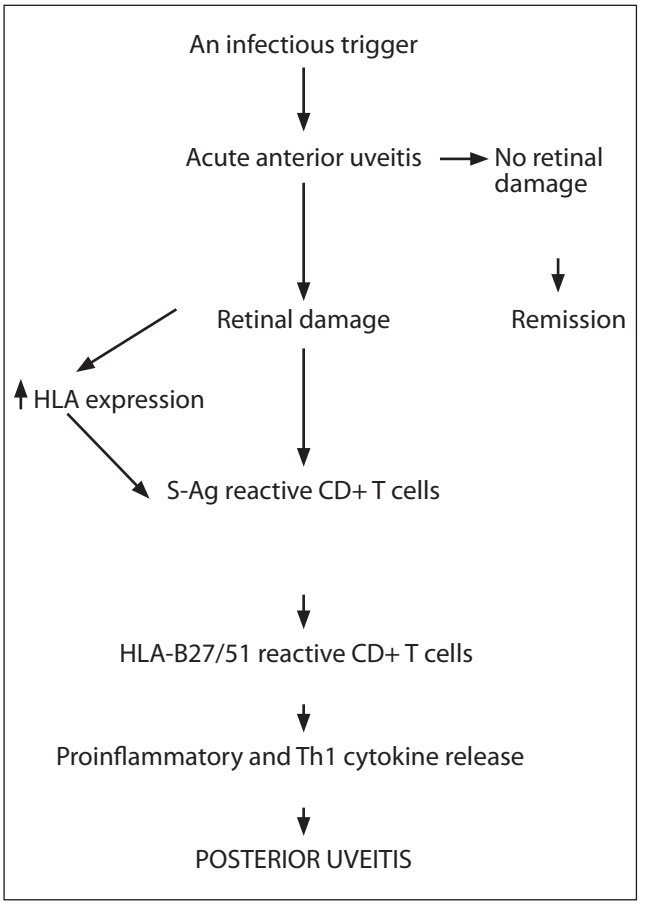
HLA-B51 association is the most important evidence for the role of genetic factors in BD pathogenesis. This association has been supported by studies on different ethnic groups. Chang et al have determined an incidence rate of 51.7% for HLA-B51 in BD and 21.4% in AS (12). Chamberlain et al have determined increased incidence of HLA-B27 in BD, which was similar to the rates determined in patients with psoriatic arthritis (6). Similarly, Lehner et al have reported increased incidence rate of HLA-B27 in BD patients with arthritis (21); however, other authors have found no association between HLA-B27 and BD and reported an incidence rate of 0-10% for HLA-B27 in BD as in normal population (22). In patients with BD, positive HLA-B27 and negative HLA-B5 have been found to constitute a risk factor for

AS development (22). Nine subtypes of HLA-B27 antigen with various aminoacid sequences have been defined. The association of AS with HLA-B2705, HLA-B2702, and HLA-B2704 has been shown in many communities (23-26). Gül et al has suggested that except HLA-B51, HLA-B2702 may be HLA-B allele associated with BD. HLA-B2702 and HLA-B51 have common sequences. This sequence is between 77-83 positions in α1 helix of HLA-B molecule. This common sequence has also been shown in KIR3DL1 (NKB1) receptor, which selectively inhibits the cellular cytotoxicity of natural killer (NK) cells. The disruption in the regulation of KIR-HLA class 1 interactions of NK and other cytotoxic T cells may account for potential pathogenic mechanisms. Nevertheless, the fact that none of the HLA-B alleles except B2702 shares B51-KIR sequence renders this hypothesis less reliable (27,28).

Retinal soluble antigen, which is a protein essentially found in the retina reflects the immune response arising after tissue destruction due to uveitis (29). Wildner et al have shown a common sequence having aminoacid homology with retinal soluble antigen in HLA-B27 and HLA-B51 (28,30). This common sequence corresponds to PDS-antigen, an immune dominant epitope of retinal soluble antigen. Against PDS-antigen of retinal soluble antigen that arises due to inflammation in the uveal tract associated with a triggering factor and retinal damage that follows, CD4 T lymphocytes become reactive and lead to expression of various proinflammatory cytokines and chemocines. The expression of these mediators increases the expression of class 1 HLA molecules like HLA-B27/51 on the surface of the uveal tract. This is followed by cross reaction of T lymphocytes that has become reactive against PDS antigen of retinal soluble antigen to the common epitope of HLA-B27/51 and retinal soluble antigen (29). At the end, increased proinflammatory cytokine expression causes tissue destruction in the uveal tract, which results in uveitis development (Diagram 1). This finding suggests that uveitis that may develop in BD and AS may have the same underlying mechanisms (27,30).

In this report, a 46-year-old patient with coexisting BD and AS, a very rare occurrence, has been presented. The patient had no marked peripheral joint involvement but axial skeletal involvement (particularly sacroiliac involvement). The case reported here seems like a coincidental BD and AS coexistence based on the clinical and laboratory findings. However, as has been mentioned in the discussion, the presence of some common sequences in the subtypes of HLA-B51 and HLA-B27 may suggest the presence of common pathways in the pathogenic process of both diseases. This may require re-questioning the hypothesis that BD should be classified in SpAs. Undoubtedly, further genetic studies on HLA-B51 and HLA- B27 will shed light on the issue.

Diagram 1. An immunological model for the role of cross reactive retinal-S antigen and HLA-B27/B51 derived protein in uveitis of Behçet's disease (Redrawn with permission from Direskeneli H (2001) Behçet's disease: infectious aetiology, new autoantigens, and HLA-B51. Ann Rheum Dis 60(11): 996-1002).



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