

CASE REPORT



Ankylosing spondylitis occurring in a patient with Behçet disease after chronic brucellosis infection: A case report and review of the literature

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Abstract

Behçet disease and ankylosing spondylitis are rarely seen together. This report presents a rare case of ankylosing spondylitis occurring in a patient with Behçet disease after chronic brucellosis infection. Infectious agents have long been considered one of the triggers for autoimmune and autoinflammatory diseases. Therefore, rheumatic processes should be kept in mind, especially in treatment-resistant cases.

KEYWORDS

ankylosing spondylitis, Behçet disease, brucellosis

1 | INTRODUCTION

Behçet disease (BD) is a disease characterized by oral and genital ulcers, involving various organs such as eyes, skin, joints, the gastrointestinal, urogenital, respiratory and central nervous systems, and blood vessels. The diagnosis of BD is made mainly on the basis of clinical symptoms and signs. Behçet disease shares some common features with autoimmune and autoinflammatory diseases and spondyloarthropathies. Multiple pathogenic pathways triggered by environmental factors such as infectious agents contribute to the development of BD in genetically predisposed individuals.¹

Axial spondyloarthritis (so-called ankylosing spondylitis, AS) is a chronic inflammatory disease that primarily affects sacroiliac joints, axial spine, peripheral joints, and entheses. It is characterized by inflammatory back pain with sacroiliitis and often arthritis of the peripheral joints, enthesitis, and/or acute anterior uveitis. Etiology is unknown but genetic predisposition, infectious agents, and environmental factors may play a role.²

In BD, involvement of large joints (such as knee, ankle, elbow, and wrist) is seen, especially in the lower extremities. Sacroiliitis is rarely seen in BD.³ Although it is very rarely defined in the literature except in case reports, the reports of BD and AS coexistence are increasing.⁴ In this report, a rare case of AS occurring in a patient with BD after brucellosis infection is presented.

2 | CASE REPORT

A 30-year-old woman was admitted to the outpatient clinic with complaints of widespread muscle and joint pain for 2 years. Her pain was more intense in both knees and arms. She complained of increasing pain by movement and relieved by rest. She also had lower back pain on rising in the morning and heel pain when she put her feet on the ground. She also had morning stiffness for about 30 minutes. She had no nausea, vomiting, decreased appetite, unintentional weight loss, abdominal pain, constipation, diarrhea, hepatosplenomegaly, or oral ulcers. She had been diagnosed with and treated for brucellosis 16 years ago. In addition, the patient was diagnosed with BD 5 years ago because of oral aphthous ulceration, genital ulcer, and a positive patergy test. After diagnosis, she had been receiving colchicine (1 mg/day). The patient had no family history of any rheumatological disease.

On physical examination, there was no limitation of lumbar spinal movement. There was no swelling or tenderness of peripheral joints. There were no objective neurological signs. Sacroiliac compression tests, FABER (flexion-abduction-external rotation of the hip) and FADIR (flexion-adduction-internal rotation of the hip) tests were positive bilaterally. Her measures of modified Schober test, chest expansion, tragus-wall distance, occiput-wall distance, and hand-ground distance were normal. The laboratory test results were

as follows: C-reactive protein 62 mg/L (0.0–5.0); erythrocyte sedimentation rate 103 mm/min (0–20); rheumatoid factor, antinuclear antibody, anti-cyclic citrullinated peptide antibody, and HLA-B27 were all negative. She had normal body temperature and no anemia (hemoglobin 12.6 g/dL) but the leukocyte count was slightly elevated (white blood cells 11 180/ μ L; normal range 4500–11 000/ μ L). Moreover, there was a positive Brucella tube agglutination test with a titer of 1/640. In the patient's history, it was determined that she consumed unpasteurized milk and dairy products. The patient was treated with doxycycline (200 mg/day) and rifampicin (600 mg/day) for 12 weeks for the brucellosis infection. She also received non-steroidal anti-inflammatory drugs (meloxicam). Plain radiographs of lumbar spine showed suspicious spinal syndesmophytes at the upper parts of the L1, L3, and L4 vertebrae corpus and suspicious sacroiliitis at the left sacroiliac joint (Figure 1). Lateral radiograph of bilateral foot and ankle showed bilateral heel spur in calcaneus but there were no erosions and there was no enthesitis (Figure 2). Magnetic resonance imaging of lumbar spine showed L3–L4 disc bulging and L4–L5 posterocentral disc protrusion. After antibiotic treatment, white blood cell count (7500/ μ L), C-reactive protein (2.31 mg/L), and erythrocyte sedimentation rate (11 mm/min) were within normal limits in her laboratory tests and her Brucella tube agglutination test was negative. However, although the widespread muscle pain was relieved, low back pain and knee pain did not resolve completely and morning stiffness continued. Therefore, sacroiliac magnetic resonance imaging was performed and the narrowing of the bilateral sacroiliac joints, more prominent on the left, was revealed (Figure 3). Moreover, inflammatory contrast enhancement was observed in the bilateral sacroiliac joint spaces, which may be compatible with the synovitic process. The patient was diagnosed with AS according to the Assessment of SpondyloArthritis international Society criteria.⁵ Then, the patient was treated with anti-tumor necrosis factor- α (anti-TNF- α , certolizumab pegol): 400 mg certolizumab pegol administered subcutaneously at weeks 0, 2, and 4, followed by 200 mg every 2 weeks. A satisfactory response was obtained with this treatment

and low back and knee pain and morning stiffness were relieved. Before the initiation of anti-TNF- α therapy, the patient was screened for tuberculosis and hepatitis. There were no complications related to the use of anti-TNF- α therapy.

3 | DISCUSSION

There are case reports in the literature on the coexistence of BD and AS^{4,6–12} as well as the coexistence of brucellosis infection and AS.^{13–15} In this report, a patient with AS after brucellosis infection found while being followed up with the diagnosis of BD is mentioned.

Brucellosis is a systemic zoonotic disease that develops as a result of hematogenous spread. It can cause different organ involvement in various ways and clinical symptoms differ. Weakness, fatigue, high fever, loss of appetite, joint pain, muscle pain, abdominal pain, headache, gastrointestinal symptoms, night sweats, and weight loss are among the symptoms of the disease. It has been reported that the most common clinical findings are fever and osteoarticular findings (back pain, arthritis, arthralgia, myalgia). Sacroiliitis is the most common musculoskeletal manifestation of brucellosis, followed by peripheral arthritis/arthralgia, spondylitis, osteomyelitis, and bursitis. The diagnosis of brucellosis requires isolation of bacteria with a blood or tissue culture or the presence of specific antibodies by an agglutination test, complement fixation test, radioimmunoassay, or enzyme-linked immunosorbent assay.¹⁶

As brucellosis frequently influences the musculoskeletal system, it is included in the differential diagnosis of various clinical pictures. It should also be noted that the treatment of both diseases is different. Musculoskeletal involvement of brucellosis usually occurs in young patients. Joint involvement patterns may suggest a spondyloarthropathy dominated by axial fibrocartilaginous joints and lower extremity diarthrodial joints, whereas spondylitis and sacroiliitis resembling AS findings can be seen in brucellosis with or without peripheral arthritis.^{13,16} The sacroiliitis of brucellosis is usually

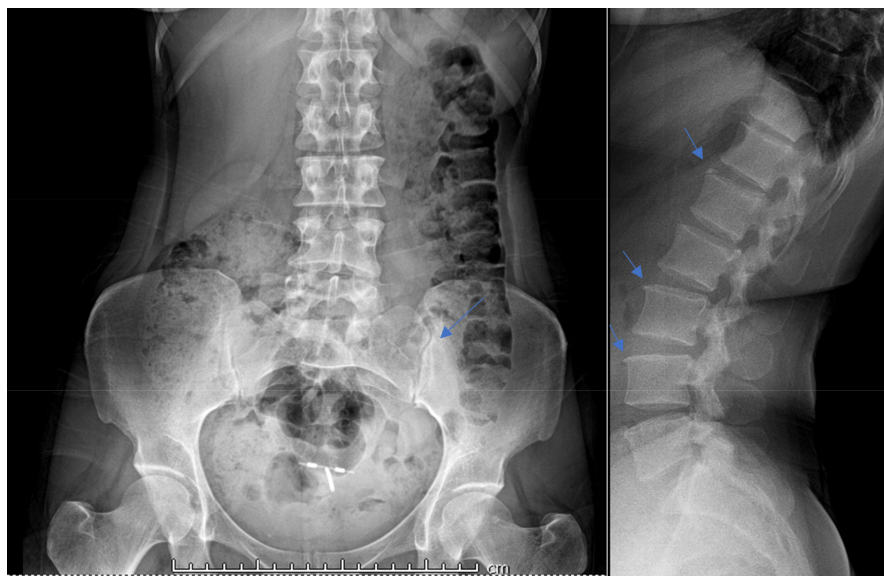


FIGURE 1 The suspicious spinal syndesmophytes at the upper parts of the L1, L3, and L4 vertebrae corpus and suspicious unilateral sacroiliitis on lumbosacral X-ray imaging



FIGURE 2 Bilateral heel spur in calcaneus on foot X-ray imaging

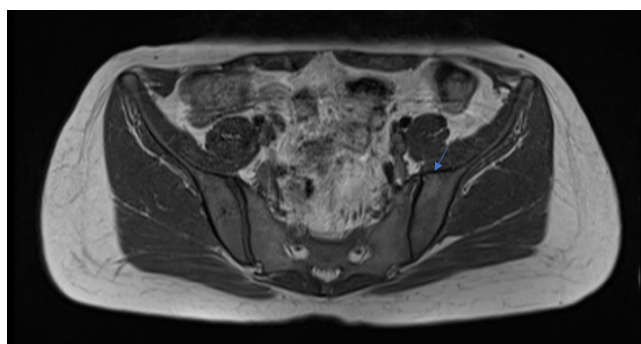


FIGURE 3 The minimal edema in the unilateral sacroiliac joints and the narrowing of the bilateral sacroiliac joints, more prominent on the left, on magnetic resonance imaging

unilateral in young patients, and it is associated with lumbar or sacral spondylitis in elderly patients. Although the diagnosis of brucellar spondylitis is difficult, it may be associated with connective tissue diseases and spondyloarthropathy. In addition, it can be difficult to distinguish changes on plain radiographs from degenerative diseases. In AS, spondylodiscitis can be seen together with sacroiliitis and is often asymptomatic. However, spondylodiscitis should be considered if pain increases after movements and improves at rest in AS. Most patients with brucella spondylitis and sacroiliitis respond to antibiotic therapy. It is suggested that the development of sacroiliitis and spondylitis in brucellosis is not associated with the presence of HLA-B27 gene.¹⁴ The patient described here had low back and knee pain that did not respond to antibiotic treatment. Moreover, both HLA-B27 and HLA-B51 were negative in this case. Therefore, sacroiliac magnetic resonance imaging was performed and the presence of unilateral sacroiliitis was revealed. A satisfactory response was obtained with anti-TNF- α therapy.

Although erosive sacroiliitis and inflammatory spinal pain are seen in BD, there is controversy over whether BD is a subgroup of

seronegative spondyloarthropathy. However, they are considered as two separate diseases. Chang et al reported a 28-year-old man who fulfilled the diagnostic criteria for both BD and AS.⁶ Borman et al reported a 29-year-old woman with coexisting BD and AS representing HLA-B27 positivity but HLA-B51 negativity. They proposed that it is reasonable to look for other diseases when the patient's clinical course is more severe than expected.⁷ Cimen et al reported a 36-year-old male patient with BD for 16 years diagnosed as having AS. They suggested that the patient may have masked the clinical features of spondyloarthropathy because of receiving medical therapy for BD.⁸ Kotevoglou reported two cases with coexisting BD and AS via atypical presentations and courses. The first patient was a 40-year-old woman with BD having syndesmophytic bridging of the cervical vertebrae, which is a typical characteristic of AS. The second patient was a 45-year-old man diagnosed with AS and BD accompanied by amyloidosis and end-stage renal failure.⁹ Albayrak et al and Nacir et al reported a patient with coexisting BD and AS demonstrating both HLA-B27 and HLA-B51 positivity.^{10,11} Yildiz et al reported a 44-year-old male patient with concomitant AS and BD who was successfully treated with anti-TNF- α therapy (adalimumab). They suggested that anti-TNF- α therapy should be considered when classical treatment modalities fail to be effective in patients with concomitant AS and BD.¹² In this case, a satisfactory response was obtained with anti-TNF- α therapy (certolizumab pegol). Characteristic features and treatments of the cases with coexistence BD and AS are summarized in Table 1.

Moreover, Frigui et al reported a 35-year-old man patient who had an association of BD, familial Mediterranean fever (FMF) and HLA-B27-positive AS.¹⁷ They proposed that spondyloarthritis should definitely be sought in case of coexistence of these diseases because it is a possible form of joint involvement in both FMF and BD. Yoo reported a 35-year-old male patient with both BD and AS, presenting with deep vein thrombosis. Although there is still a debate about the coexistence of BD with AS, they suggested that it may be a very rare rheumatic disease entity and venous thrombosis may be a vascular complication.⁴

Ardic et al reported a female patient with a known diagnosis of brucellosis from 1 year who developed AS with HLA-B27 positivity.¹³ Özeri et al reported a female case with concomitant AS and brucellosis who was misdiagnosed with spondylitis and sacroiliitis due to brucellosis, because of similar spinal involvement.¹⁴ Both Ardic and Özeri and their co-workers proposed that physicians should always keep in mind the coexistence of AS and brucellosis in endemic areas and the diagnosis of brucellosis alone should not always be considered satisfactory, especially in patients that are resistant to treatment.^{13,14} Akyol et al. reported a female case with co-morbidity of sacroiliitis and brucellosis infection diagnosed with uveitis. Although the patient was treated with doxycycline and rifampicin for brucellosis infection and with acetaminophen for AS, the uveitis was not controlled by this so the patient was given infliximab. They suggested that uveitis was due to reactivation of AS caused by brucellosis because the patient's inflammatory joint symptoms and eye symptoms had continued for about 4 years.¹⁵ Behçet disease is thought to be a dysregulated immune

TABLE 1 Characteristics and treatments of our case and previous case reports of concomitant AS and BD in the literature

Author	Age (y)	Gender	HLA-B51	HLA-B27	Treatment
Chang et al ⁶	28	Male	(+)	(+)	NSAID, sulfasalazine, methotrexate, colchicine
Borman et al ⁷	29	Female	(-)	(+)	NSAID, sulfasalazine, systemic corticosteroid
Cimen et al ⁸	36	Male	(+)	(+)	NSAID, cyclophosphamide, systemic corticosteroid
Kotevoglul et al ⁹	45	Male	NA	(+)	NSAID
Kotevoglul et al ⁹	40	Female	(+)	(+)	NA
Yoo et al ⁴	35	Male	(+)	(-)	NSAID, sulfasalazine
Albayrak et al ¹⁰	33	Female	(+)	(+)	NSAID, sulfasalazine, colchicine, intra-articular corticosteroid
Nacir et al ¹¹	46	Male	(+)	(+)	NSAID, sulfasalazine, colchicine
Yildiz et al ¹²	44	Male	(+)	(-)	Anti-TNF- α (adalimumab)
This case	30	Female	(-)	(-)	Anti-TNF- α (certolizumab pegol)

Abbreviations: AS, Ankylosing spondylitis; BD, Behçet disease; NA, not available; NSAID, non-steroidal anti-inflammatory drug; TNF- α , tumor necrosis factor- α .

response triggered by an environmental antigen, such as a virus or bacterium, that occurs in individuals who are genetically predisposed to the disease.¹ Moreover, the association of infectious agents with the development of autoimmune diseases is well known. It is possible that the combination of certain genes and certain infectious exposures leads to the development of an autoimmune disease. Infectious agents involved in a series of events critical to the onset of autoimmunity and the development of autoimmune disease can be tracked at various time points. Infections at different times, which are responsible for the chain reaction of events leading to autoimmune disease, may participate in the clinical patterns of remission and relapse seen after the onset of the disease.¹⁸ In this case, it can be thought that the development of both BD and AS may be related to brucellosis.

4 | CONCLUSION

Infectious agents have long been considered one of the triggers for autoimmune and autoinflammatory diseases, mainly through promoting the production of autoantibodies and cytokines through molecular mimicry and the induction of protein changes and bystander activation via epitope spreading.¹⁹ Microbiological examination for brucellosis should be requested in patients presenting with joint and musculoskeletal complaints in endemic areas. Moreover, rheumatic processes should be kept in mind, especially in treatment-resistant cases.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this paper.

INFORMED CONSENT

Informed consent was obtained from the patient.

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