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CASE REPORT

Kota Sugisaki · Shinji Ogasa · Syuji Okubo

A case of possible Behçet's disease, preceded by recurrent knee arthropathy for 5 years, effectively treated with oral colchicine

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Abstract We report a case of possible Behçet's disease (BD) preceded by arthropathy for 5 years. A 29-year-old man experienced right knee swelling and pain since April 1999. Thorough examinations were performed, yet a diagnosis was not established. In December 2004 he experienced recurrent aphtha, following folliculitis-like skin lesions. A human leukocyte antigen examination revealed a positive B51 allele and his illness was diagnosed as possible Behçet disease. Colchicine was administered and his symptoms were ameliorated.

Key words Arthropathy · Behçet's disease (BD) · Colchicine · HLA-B51 · Osteonecrosis

Introduction

Behçet's disease (BD) is a systemic syndrome of unknown etiology, characterized by aphthae, genital ulcers, ocular lesions, and folliculitis-like skin lesions. The close association of BD and the HLA-B51 allele has been widely recognized. Behçet's disease often accompanies arthritic symptoms such as joint pain, swelling, and synovial fluid collection. In some reports, the arthritic symptoms are the initial symptoms of BD and the arthritic symptoms precede the typical BD symptoms by several weeks to several months. It is rare that arthritic manifestations precede the typical BD symptoms for a year or more.

In this case report, we describe an HLA-B51-positive patient who developed bilateral knee arthropathy preceding an aphtha and skin lesions. The arthropathy preceded typical BD symptoms by approximately 5 years. Although the condition of the patient did not fulfill the diagnostic criteria of BD sufficiently, oral colchicine was administered and seemed to be effective. The correlation of the arthropathy of unknown etiology and BD is discussed.

K. Sugisaki (✉) · S. Okubo
Division of Internal Medicine, Kasukabe Central General Hospital, 5-9-4 Midori-cho, Kasukabe 344-0063, Japan
Tel. +81-48-736-1221; Fax +81-48-738-1559
e-mail: drsugi@s3.dion.ne.jp

S. Ogasa
Division of Dermatology, Kasukabe Central General Hospital, Kasukabe, Japan

Case report

A 29-year-old man visited the Division of Orthopedics in our hospital on April 10, 1999 with right knee pain and swelling that began several days earlier. Seven years previously, he was hospitalized at another hospital for high fever and abdominal pain of unknown cause and antiphospholipid antibody syndrome was diagnosed, although the details of the clinical course were indistinct. Although the patient played rugby in his high school days, his current employment involved deskwork. He had no siblings and his parents had no history of particular disorders. He had no history of alcohol abuse and he did not take any drugs. On the first medical examination, the patient's right knee was mildly swollen without redness or local heat. A moderate amount of synovial fluid had collected and floating patella was observed. The range of movement in his knees was satisfactory; however, he reported stress pain upon extension. A simple X-ray showed slight and even narrowness in the right knee joint space without erosive and destructive changes. Calcification of the meniscus was not observed. Yellowish, non-bloody synovial fluid (50 ml) was aspirated. No crystals were detected in the aspirated synovial fluid. The white blood cell count in the synovial fluid was not increased. A mucin clot test was not performed. The synovial fluid culture was negative. Although the history of external trauma was not distinct, a meniscus injury was suspected and the knee was treated with 225 mg/day of mofezolac. No blood and urine examinations were performed.

After this, the patient visited our hospital approximately once every 2 months. In spite of the treatment, his right knee involvement often flared up and ameliorated sponta-

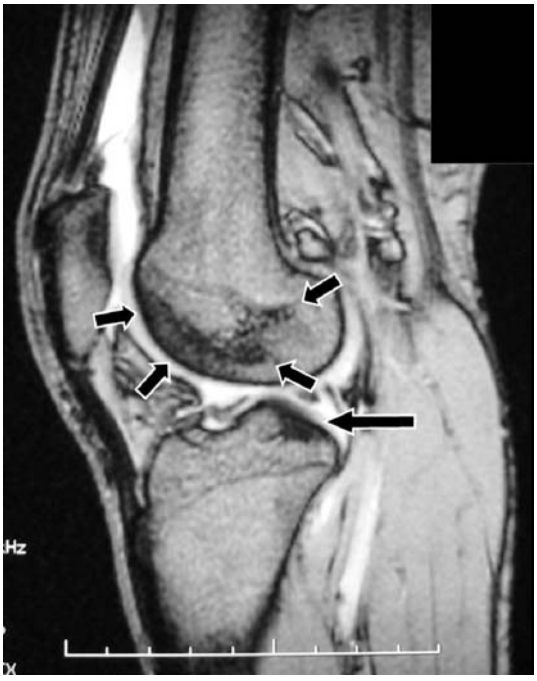

Fig. 1. Sagittal T1-weighted magnetic resonance images of the patient's right knee taken on April 28, 2001, showed an irregular low-intensity area in the distal femur and a partial low-intensity lesion in the lateral tibia plateau (*arrows*) with a small amount of synovial fluid

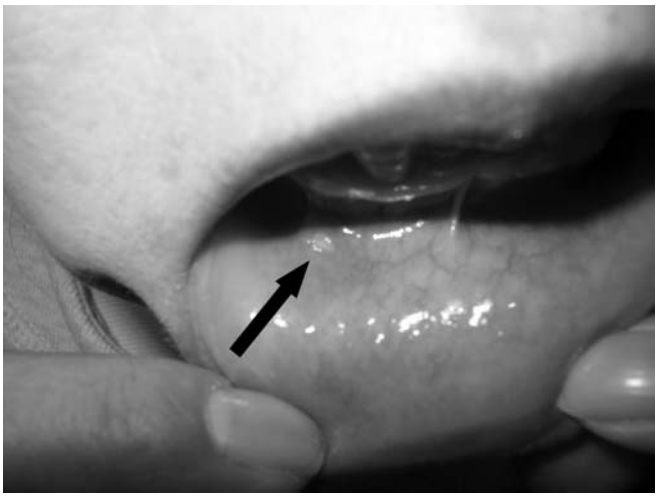

Fig. 2. A single aphtha was noted on the lower lip (*arrow*)

neously within 2 weeks. He repeatedly received synovial fluid aspiration with further examination and injection of sodium hyaluronate frequently; nothing new was found. In July 1999, physicians suggested that the patient undergo an arthroscopic synovectomy; however, the patient did not accept the suggestion, so the surgery was not performed. Although intra-articular injections of 4 mg betamethasone were begun in September 1999, his right knee symptoms were not ameliorated and continued to flare up sporadically. On April 21, 2001, the first blood examination was performed. The laboratory data obtained were as follows: white blood cell count, 9200/μl (normal, 4000–8500/μl) with no abnormal hemogram levels; hemoglobin, 14.8 g/dl (normal, 13.5–17.5 g/dl); platelets, 26.6×10^4/μl (normal, 12–36 × 10^4/μl); uric acid, 8.0 mg/dl (normal, <7.0 mg/dl); and C-reactive protein (CRP), 0.7 mg/dl (normal, <0.5 mg/dl). No hepatorenal damage was observed. Rheumatoid factor was negative. Magnetic resonance imaging (MRI) of the patient's right knee taken on April 28, 2001, showed an irregular low-intensity area in the distal femur and a partial low-intensity lesion in the lateral tibia plateau; degenerative change was suspected (Fig. 1). Blood examination data taken on February 6, 2003 were as follows: CRP, 0.5 mg/dl; erythrocyte sedimentation rate, 12 mm/h (normal, 1–7 mm/h); uric acid, 7.1 mg/dl; and matrix metalloproteinase-3 (MMP-3), 307 ng/ml (normal, 36.9–121 ng/ml). Recurrent gout attacks or seronegative rheumatoid arthritis (RA) was suspected, and treatment with 100 mg/day of allopurinol and 0.5 mg/day of colchicine was begun on June 10, 2003. However, the patient discontinued his regular visits to our hospital in October 2003 because his work kept him busy. The orthopedist suspected pigmented villonodular synovitis, but the diagnosis was not established.

In December 2004 the patient began experiencing a recurrent aphtha, following folliculitis-like skin lesions in his back and lower extremities. A single aphtha appeared with mild pain and disappeared within 2 weeks without any special treatment. Because these symptoms were not especially severe, he did not request special treatment. Around the end of February 2005, in addition to his right knee, his left knee swelled with pain; 90 ml of yellowish synovial fluid was aspirated. Local heat and redness were not observed in the left knee as had been observed in the right knee. On March 7, 2005 he was referred to the Division of Internal Medicine for an examination for rheumatic disease.

On the first visit to our division, the patient's chief complaint was bilateral knee swelling and pain. His height was 174 cm and his weight was 67 kg. He was afebrile and showed no signs of malar rash, Raynaud's phenomenon, photosensitivity, or alopecia. A single aphtha on his lower lip was noted (Fig. 2). Folliculitis-like eruptions with slight pigmentation were noted on his back, hip, and lower extremities (Fig. 3). No genital lesions such as ulceration were noted. No signs of deep vein thrombosis were observed. The ophthalmologic investigation revealed no abnormal findings, such as iridocyclitis and chorioretinitis.

Laboratory data were as follows: total cholesterol, 205 mg/dl (normal, 130–219 mg/dl); triglycerides, 120 mg/dl (normal, 30–149 mg/dl); hemoglobin A1c, 4.9% (normal, 4.3%–5.8%). Urinalysis was normal. No antinuclear, anti-DNA, anti-Sm, anti-Ro, anti-La, or antigalactose-deficient immunoglobulin G antibodies were detected and no anticardiolipin/β2-glycoprotein I complex antibody was detected. Lupus anticoagulant tested by the diluted Russell's viper venom time method was also negative. The levels of soluble interleukin (IL)-2 receptor and tumor necrosis factor-α (TNF-α) in synovial fluid aspirated from the patient's right knee were 362 U/ml and less than 5 pg/ml, respectively.

Fig. 3. Folliculitis-like eruptions with slight pigmentation were noted on the patient's feet

The HLA-B loci determined by a conventional serological method were B51 and B52.

Possible Behçet's disease was diagnosed on the basis of the criteria from the Behçet's Disease Research Committee of Japan (1987 revision). On June 21, 2005, the oral administration of 1 mg/day of colchicine was started and the patient was carefully instructed to continue regular oral administration. He visited our hospital on August 23, 2005, experiencing only mild discomfort in both knees without swelling or local heat. He reported that the aphtha had never reappeared since around the beginning of July 2005; however, the skin lesions slightly remained. The CRP level at that time was 0.1 mg/dl.

Discussion

Generally, arthropathy is frequently seen in BD cases. Involvements of the knees, ankles, and wrists are most common.[1] Conversely, patients with BD who initially experienced arthritic symptoms are relatively rare. Pipitone et al. reported that 14.2% of patients with BD reported symptoms of arthritis at disease onset.[2] In Japan, several cases of patients with BD who first experienced arthritis have been reported. These patients initially experienced arthritis in their knees or sacroiliac joints, and the major BD symptoms such as erythema nodosum, genital ulcers, and recurrent aphtha followed within several months. Although this case has not yet been conclusively diagnosed, it is rare that a patient with arthropathy of unknown etiology would experience BD-like symptoms more than 1 year later.

Careful consideration as to whether the patient's arthropathy was related to BD is required. Although meniscus damage was temporarily suspected, the episode of the external trauma was indistinct and meniscus damage was not evident on X-ray and magnetic resonance imaging (MRI) films. On the other hand, the intensity change inside the bone on MRI was conspicuous. This finding coincided with the aseptic osteonecrosis that was occasionally seen in cases of other rheumatic diseases, especially systemic lupus erythematosus (SLE) and RA. Aseptic osteonecrosis, one of the important complications in rheumatic diseases, is considered to be caused by voluminous and long-term steroid administration,[3] vascular fat embolism owing to hyperlipidemia,[4] excessive alcohol intake,[5] systemic vasculitis,[6–8] or antiphospholipid antibody syndrome.[9–11] In the present case, the patient did not receive systemic steroidal administration and the MRI showing osteonecrosis was taken before any intra-articular steroidal injection. Moreover, the patient was not diabetic and hyperlipidemia was not evident. The patient had no history of alcohol abuse. Meanwhile, several cases of BD with severe destructive arthropathy have been reported,[12,13] although the arthropathy in BD has been regarded as usually not destructive. Although identification of the cause of the osteonecrosis in this case was difficult, it might be most plausible that the osteonecrosis in this case was relevant to possible BD for the abovementioned reasons. Pigmented villonodular synovitis should be differentiated because this disease frequently appears in juvenile patients and affects knee joints with a high frequency. Although a synovial biopsy was not performed, pigmented villonodular synovitis was not plausible because the synovial fluid was not bloody and MRI showed no nodular or tumorous lesions in the synovium. Additionally, SLE was not plausible because of the absence of specific symptoms such as malar rash and the negative results for autoantibodies such as anti-DNA antibody.

At one time, the present case was suspected to be seronegative RA because of the high titer of serum matrix metalloproteinase (MMP)-3. The serum MMP-3 level was easily measured by using a commercial kit and is widely understood as a quantitative marker of the activity of synovitis,[14] especially in RA. Although, to the best of our knowledge, no cases of BD with high titers of MMP-3 have been reported, the diagnosis of BD was more plausible than that of RA because of positive HLA-B51 results and the symptoms suggesting BD that appeared later. Ertenli et al. reported that the levels of TNF-α and soluble IL-2 receptor in synovial fluid were significantly higher in cases of RA than in cases of BD.[15] They showed that the mean synovial fluid TNF-α level in patients with RA was 360 pg/ml while the level in patients with BD was only 4.4 pg/ml. In the present case, levels of both cytokines were not significantly high and the synovial fluid TNF-α level closely resembled that of the BD patient group in the report by Ertenli et al.[15] The diagnosis of RA was also not plausible from this result. Antibodies directed against cyclic citrullinated peptides (anti-CCP antibodies) have recently been measured for the

differential diagnosis of RA from the other arthritic syndromes;[16,17] however, it was not measured in this case.

In the present case, colchicine seemed to be effective as in other BD cases. The reason for the ineffectiveness of colchicine prescribed on June 2003 was indistinct; however, the possibilities that the prescribed amount of colchicine was insufficient and that drug intake was irregular should be considered. In this case, regular daily administration of colchicine seemed to be effective in relieving the symptoms.

In conclusion, we reported the case of a patient who experienced BD-like symptoms such as aphtha and folliculitis-like eruptions, preceded by recurrent arthropathy of unknown origin for approximately 5 years, successfully treated with colchicine. An HLA locus examination was useful for diagnosing the patient's illness, and measurement of the levels of cytokines in the synovial fluid facilitated the differential diagnosis from RA. Colchicine showed clinical efficacy as in typical cases of BD. Behçet disease should be considered when a young patient experiences arthropathy of unknown etiology, even if typical BD symptoms are absent.

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