Osteonecrosis and bone infarction in association with Behcet's disease: Report of two cases

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ABSTRACT

We describe two cases with Behcet's disease (BD) developing osteonecrosis or bone infarction. One patient developed the extensive bone infarction of the left knee without the use of corticosteroids. The other patient had osteonecrosis at the right femoral head. He had had a past history of significant corticosteroid administration to treat several complications of BD such as central nervous system involvement, uveitis, gastrointestinal involvement, and pulmonary involvement. Anticardiolipin (aCL) antibodies were positive in these two patients. One was IgG type, and the other was IgM type. However, it remains unclear that there is relationship between the presence of aCL antibodies and occurrence of osteonecrosis.

Introduction

Osteonecrosis is defined as the death of bone marrow and trabecular elements from repeated interruptions or a single massive interruption of the blood supply to the bone (1). By convention, the term of osteonecrosis is generally applied to areas of epiphyseal or subarticular involvement, whereas the term of bone infarction is usually reserved for metaphyseal or diaphyseal involvement (2). It is a debilitating disease affecting patients primarily in the 3rd through 5th decades of life (3). Osteonecrosis or bone infarction complicated in BD has been rarely reported in the literature (4). We describe two cases developing osteonecrosis or bone infarction in association with BD. The aCL antibodies were positive in these two patients. The occurrence of aCL antibodies in BD will be discussed.

Case reports

Case 1

A 45-year-old woman presented with sudden severe pain of the left knee. She has been suffering from recurrent oral ulcerations and genital ulcerations for past ten years. Since five years ago, she has had recurrent erythema nodosum-like lesions at the lower extremities. But she has never taken any specific medications for her illness. There was no past history of smoking, use of oral contraceptives, or abuse of alcohol.

Physical examination revealed multiple aphthous ulcers on the buccal mucosa and erythema nodosum-like lesions on the anterior aspect of both lower legs. The pathergy test was positive. There was tenderness over the medial aspect of the left knee, but no swelling or limitation of motion.

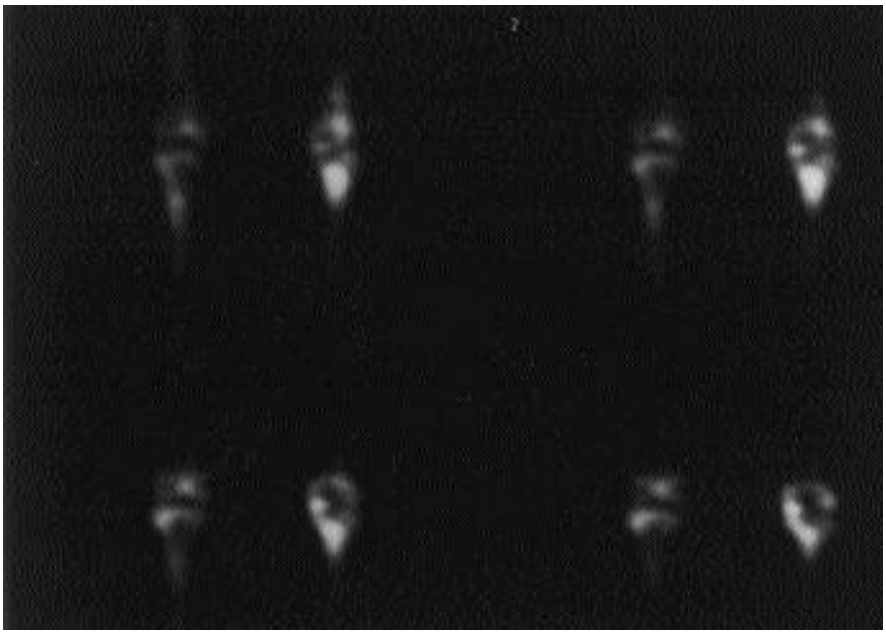
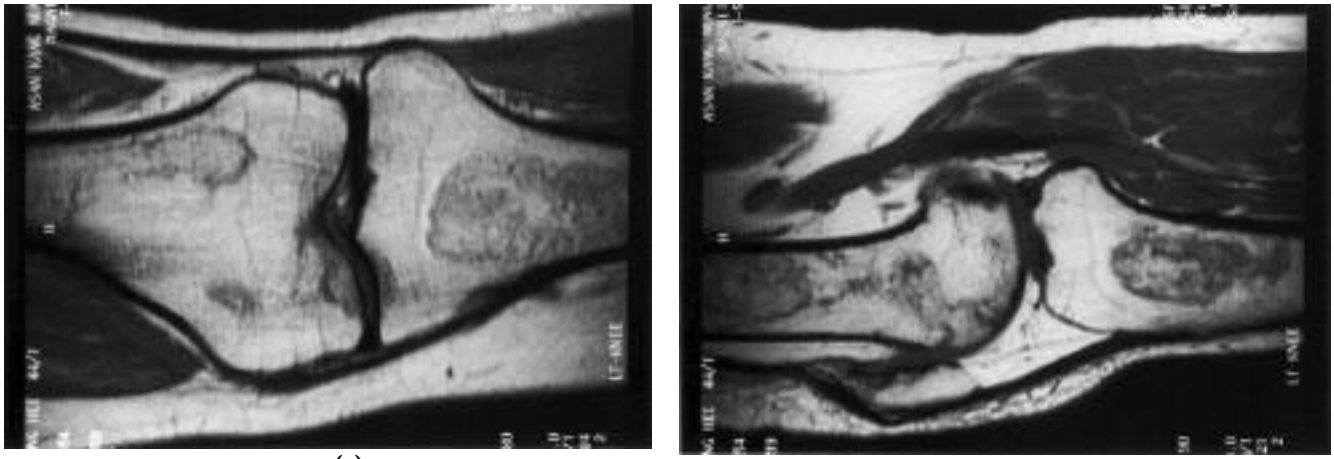


Fig. 1. The coronal images of bone single photon emission computed tomography shows a large cold defect of bone uptake over the proximal tibia and distal femur with surrounding increased bone uptakes, suggesting bone infarction.



(a) (b)

Fig. 2. Proton-density weighted, coronal (a) and sagittal (b) scans of the left knee show extensive marrow lesions at the proximal tibia and distal femur that are compatible with bone infarction.

Hematological and biochemical tests were as follows: WBC 10200/mm^3, hematocrit 39.3%, platelet 370000/mm^3, total protein 6.1 g/dl, albumin 3.6 g/dl, AST 14 IU/l, ALT 26 IU/l, creatinine 0.8 mg/dl, cholesterol 202 mg/dl, alkaline phosphatase 117 IU/l. Erythrocyte sedimentation rate was 10 mm/hour and C-reactive protein was negative. Urinalysis and coagulation tests were normal. Rheumatoid factor and antinuclear antibody were negative. IgG aCL antibody was 18 U GPL/ml (normal upper limit; 10 U GPL/ml). IgM aCL antibody and lupus anticoagulant test were negative. HLA-B51 antigen was positive. There were no specific abnormalities on plain radiograph of the left knee. Bone single photon emission computed tomography (Fig. 1) and magnetic resonance imaging (Fig. 2) of the left knee showed extensive bone infarction at the proximal tibia and distal femur.

She was diagnosed as BD with bone infarction of the left knee. A period of rest with static quadriceps exercise for 2 weeks was recommended. Initially colchicine 1.2 mg daily, aspirin 100 mg daily and nabumetone 1000 mg daily were prescribed. After that, her knee joint pain has subsided. This was followed by a gradual return to normal activity without complications of the left knee.

Case 2

A 30-year-old man presented with right hip pain. He has had recurrent oral ulcerations, recurrent scrotal ulcerations, papulopustular eruptions and erythema nodosum-like lesions for past 5 years. Three years ago, bilateral posterior uveitis had developed. Even though treating with high dose corticosteroid at the private ophthalmologic clinic, his vision of the left eye was lost. Two and half years ago, he was admitted to the university medical center due to seizure and multiple cerebral infarction, and was diagnosed as neuro-Behcet's disease. At that time, while being treated with high dose corticosteroid and azathioprine, he had right hemicolectomy for intestinal hemorrhage, and multiple perforations of cecum and ascending colon. After recovery, he had been treated with low dose prednisolone and azathioprine for 2 years. Seven months ago, he was admitted to our hospital with complaints of high fever and dyspnea. The diagnosis of pulmonary infarction associated with BD was established. His disease was improved with high dose corticosteroid and cyclosporine. After discharge, low dose prednisolone and cyclosporine were prescribed.

On examination, there were multiple aphthous ulcers of the buccal mucosa and gingiva, several pustular eruptions on the cheek and anterior chest. Decreased range of motion and positive Patrick test of the right hip were noted. The pathergy test was positive.

Laboratory test results were as follows: WBC 7100/mm^3, hematocrit 38.9%, platelet 202000/mm^3, total protein 6.6 g/dl, albumin 3.9 g/dl, AST 12 IU/l, ALT 9 IU/l, creatinine 1.0 mg/dl, cholesterol 154 mg/dl, alkaline phosphatase 124 IU/l, erythrocyte sedimentation rate 7 mm/hr, C-reactive protein < 0.8 mg/dl, rheumatoid factor negative, antinuclear antibody negative, coagulation test and urinalysis normal, HLA-B51 positive, IgM aCL antibody 15 U MPL/ml (normal upper limit; 7 U MPL/ml), IgG aCL antibody and lupus

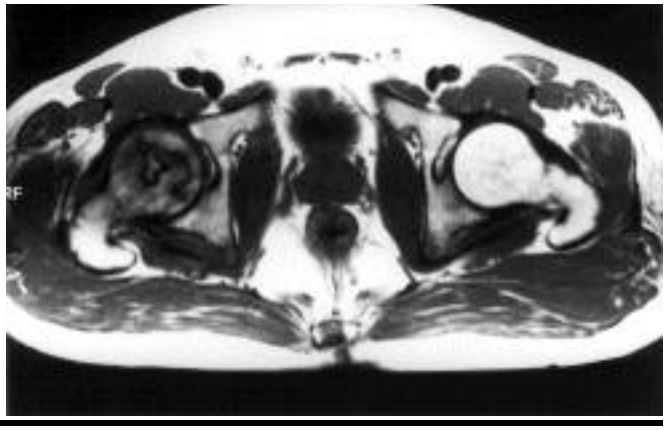


Fig. 3. T1-weighted axial magnetic resonance image shows geographic, dark signal intensity line at the superomedial portion of right femoral head, suggesting osteonecrosis with bone marrow edema.

anticoagulant negative. There were osteonecrosis at the superomedial portion of right femoral head on magnetic resonance imaging (Fig. 3). Total joint arthroplasty of the right hip was performed. He had uneventful recovery.

Discussion

BD is a chronic inflammatory disorder with multisystem involvement characterized by oral ulcers, genital ulcers, uveitis and skin lesions, most likely occurring with the underlying vasculitis. There may be other organ involvement of joints, heart and lungs as well as neurological and gastrointestinal involvement. There are no specific diagnostic and laboratory tests for BD. The diagnosis of BD mainly depends upon the thorough history taking and clinical manifestations. Our two cases fulfilled the diagnostic criteria of BD by the International Study Group for Behçet's disease (5).

One of the most important risk factors for the development of osteonecrosis involves the use of oral corticosteroids. The risk increases more with the cumulative corticosteroid total dose rather than the daily dose (6). Other risk factors include alcohol abuse, systemic lupus erythematosus (SLE), sickle cell disease, Gaucher's disease, disbaric conditions, trauma, and malignant disorders (1,7). Although the corticosteroids have been commonly used for the treatment of active BD, osteonecrosis or bone infarction associated with BD have been rarely reported in the literature. Apart from BD, patients with SLE in whom corticosteroids are also widely used are at especially high risk for the development of osteonecrosis (8-10). The incidence of osteonecrosis in patients with SLE has variably noted. Mont MA *et al.* (8) found 31 cases of osteonecrosis in 103 patients (30%). They also found that maximal predinisone doses, IgG aCL levels, and clinical evidence of venous thrombosis and vasculitis were associated with osteonecrosis. However, the risk factors and incidence of osteonecrosis in patients with BD have been still unknown. In our report, case 1 developed extensive bone infarction of the left knee without the use of corticosteroids, but case 2 had past history to be administered high cumulative doses of corticosteroid to treat the serious complications of BD.

The prevalence of IgG or IgM aCL antibodies in patients with BD has been variably noted in ranging from 18.6% to 46.7% (11-15). A few studies showed that the occurrence of aCL antibodies in patients with BD had a positive correlation with some clinical manifestations such as erythema nodosum or retinal vascular disease (11, 12). However, other studies found that aCL antibodies did not play a major role in the pathogenesis of BD or in the development of some clinical manifestations such as vascular complications or central nervous system manifestations (13-15).

Some studies showed that the level of aCL antibodies in BD patients was not only lower than one in patients with SLE, but also anti-ß2-glycoprotein I antibody (aGPI) which may be required for binding of aCL to cardiolipin was not detected (14, 16-18). The aGPI may be more strongly associated with thrombosis than aCL in patients with SLE (19, 20). These could be the reasons why the prevalence of osteonecrosis in BD patients may be lower than that in patients with SLE. The higher level of IgG aCL seems to have more clinical significance (21,22). The clinical consequences of IgM aCL or lower level of IgG aCL remain controversial. However, lower levels do not preclude the clinical significance (23, 24). In current cases, the level of aGPI was not measured. Although aCL levels in our patients were low, aCL level in case 2 was measured during the administration of corticosteroid and immunosuppressive agents. Temporary elimination or reduction of aCL antibodies may be accomplished by high dose corticosteroid or immunosuppressive agents (25).

Asherson *et al*. described two patients with primary antiphospholipid syndrome who developed osteonecrosis of the femoral head in the absence of past steroid administration (26). In addition, Korompilias *et al*. reported the increased prevalence of aCL antibodies in patients with nontraumatic osteonecrosis of the femoral head (24). However, there have been no reports about the relationship between aCL antibodies and the occurrence of osteonecrosis or bone infarction in patients with BD. Differently from case 2, case 1 did not have any known risk factors for ostenecrosis or bone infarction except positive aCL antibody. Because it remains uncertain whether aCL antibodies are simple phenomena secondary to the disease process or they could play some role in the pathogenesis of osteonecrosis, more studies and experience will be needed.

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