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Case Report

The First Case of Multifocal Osteonecrosis in Behcet's Disease

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Abstract

Background: Osteonecrosis is death of bone tissue due to interruption of the blood supply. It can occur in autoimmune disease due to multiple mechanisms. It occurs rarely in some kind of multisystem disease such as Behcet's disease (BD). The aim of this article is to present a case of BD with multifocal osteonecrosis.

Case Presentation: A 26-year-old woman with oral aphthosis, panuveitis, and retinal vasculitis was diagnosed to have BD, and oral treatment of prednisolone (0.5 mg/kg/day) together with azathioprine (2 mg/kg/day) and intravenous (IV) cyclophosphamide (CYC) (0.75 g/m^2) was administered for her. Prednisolone was tapered to 15 mg/day after 3 months. Because of unresponsiveness of eye involvement to traditional immunosuppressive therapy, infliximab (5 mg/kg) was started for her and IV CYC was discontinued. 4 months after initial therapy, she complained of her right shoulder pain. Regarding to shoulder pain, magnetic resonance imaging (MRI) showed osteonecrosis of right shoulder. After diagnosis of osteonecrosis, prednisolone was discontinued by herself. 3 months later, she complained of both knees, both hips, and right ankle pain. According to previous diagnosis of osteonecrosis of her right shoulder, MRI was done for all involved joints, which revealed osteonecrosis of all of them. After diagnosis of multifocal osteonecrosis, the following tests were done that all results were normal: anticardiolipin antibody (ACA) [immunoglobulin G (IgG), immunoglobulin M (IgM)], lupus anticoagulant (LA), anti-beta-2 glycoprotein 1 (antiB2GP1) (IgG, IgM), coagulation tests, and lipid profiles.

Conclusions: Bone infarction should be considered in differential diagnosis of patients with joint pain and without the evidence of arthritis; however, it rarely occurs in patients with BD.

Keywords: Behcet's Disease; Osteonecrosis; Avascular Necrosis of Bone

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Background

Behcet's disease (BD) is a kind of multisystem disease which is classified as vasculitis. It is characterized by oral and genital apotheosis and cutaneous, ophthalmic, neurologic, or rheumatologic manifestations. Patients with BD who have severe organ involvement such as ocular abnormalities require systemic corticosteroid in combination with other immunosuppressive agents. The prevalence, and often the severity of BD, is high in the Middle East and the Mediterranean region (i.e., the "Silk Route") (1-3).

Osteonecrosis is defined as the death of bone marrow and trabecular elements due to the interruptions of blood supply to the bone. Some proposed mechanisms for osteonecrosis include endothelial dysfunction, abnormal angiogenesis, and repair mechanisms (4). Multiple mechanisms may occur simultaneously, and concept of cumulative stress was introduced (5). The strength of a causal relationship varies greatly and in some disease, such as BD, only a few numbers of case reports have been published (6-9). The aim of this article is to present a case of BD with multifocal osteonecrosis as the first case in the world.

Case Presentation

A 26-year-old woman was referred to our BD clinic in Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, with decreased visual acuity for 2 weeks in her both eyes. Oral apotheosis was also an accompanying complaint which was started 5 months before eye involvement. Ophthalmologic examination disclosed panuveitis and retinal vasculitis in both eyes. Patient had no history of joint pain or other past medical history. Pathergy test was negative. According to International Criteria for BD (ICBD), she was diagnosed to have BD and thereupon, oral prednisolone (0.5 mg/kg/day) together with azathioprine (2 mg/kg/day) and intravenous (IV) cyclophosphamide (CYC) (0.75 g/m^2) were administered for her. Prednisolone was tapered to 15 mg/day after 3 months of treatment onset. Because of the unresponsiveness of eye involvement to traditional immunosuppressive therapy, infliximab (5 mg/kg) was started for her and IV CYC was discontinued. 4 months after initial therapy, she complained of right shoulder pain. Therefore, magnetic resonance imaging (MRI) was planned which elicited osteonecrosis of right shoulder (Figure 1).

After diagnosis of osteonecrosis, prednisolone was discontinued by the patient. 3 months later, she complained of pain in her both knees, both hips, and right ankle, which was aggravated by ambulation. According to previous diagnosis of osteonecrosis of her right shoulder, MRI was one in order to investigate the involved joints, which then revealed the osteonecrosis of all of them (Figures 2-6).

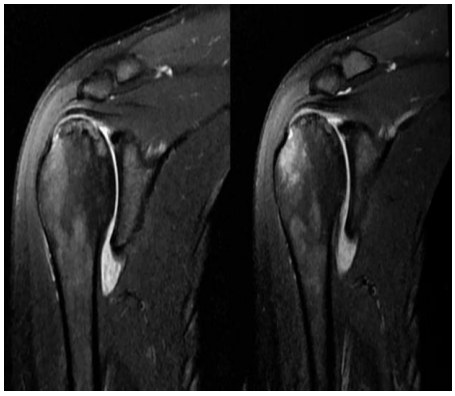

Figure 1. Coronal fat-suppressed T2-weighted image of right shoulder shows abnormal signal in the humeral head associated with bone marrow edema and subchondral fracture suggesting avascular necrosis (AVN) of humeral head. Mild joint effusion is also depicted.

After diagnosis of multifocal osteonecrosis, the following laboratory tests were done and their results came back normal: anticardiolipin antibody (ACA) [immunoglobulin G (IgG), immunoglobulin G (IgM)], lupus anticoagulant (LA), anti-beta-2 glycoprotein 1(antiB2GP1) (IgG, IgM), coagulation tests, and lipid profiles.

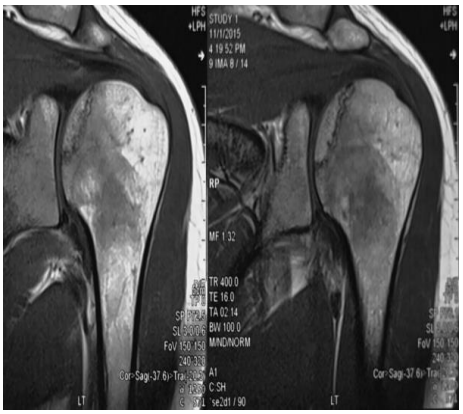

Figure 2. Sagittal T1-weighted image of left shoulder shows avascular necrosis (AVN) of left humeral head associated with subchondral fracture and diffuse bone marrow edema.

Discussion

Our case was a rare presentation of osteonecrosis in a patient with BD. Occurrence of multifocal osteonecrosis in BD has not been reported so far.

BD is a kind of vasculitis disease. Vasculitis is a principal pathological finding in BD and vessels of all sizes, both in arterial and venous systems, may be involved. The role of endothelial dysfunction in pathogenesis of BD is determined by lower level of prostacyclin and higher level of nitric oxide (NO) in serum of patients with BD -which may play a role in endothelial activation- resulting in vascular inflammation and thrombosis (10). Anti-endothelial cell antibodies (AECAs) have been detected in serum of patients with BD and have been associated with disease activity and vasculitis symptoms.

There is a significant thrombotic tendency in the vascular involvement of BD (11). The etiology of thrombosis in BD is largely unknown; however, the role of prothrombotic factors, abnormal fibrinolysis, and platelet dysfunction has been considered, but no significant associations have been noted (12).

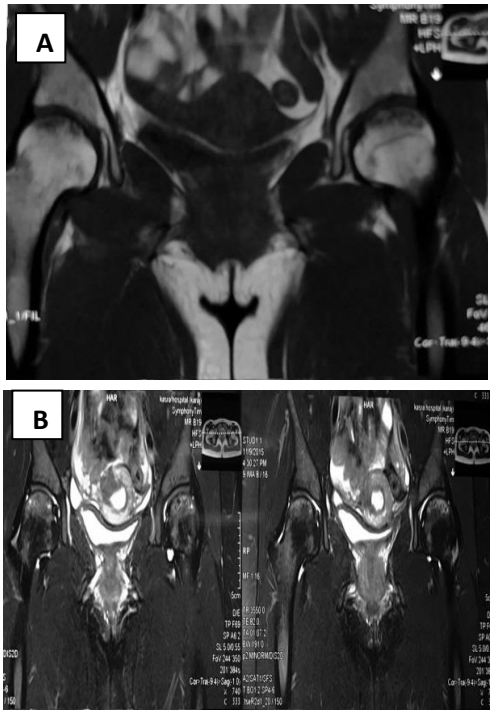

Figure 3. Coronal T1 (A) and T2 (B) weighted image of bilateral hip shows avascular necrosis (AVN) of femoral head associated with mild bilateral joint effusion.

Vessel wall inflammation leading to endothelial damage is considered as the most conceivable cause of thrombosis, which makes immunosuppressive therapy authorized; even though, Seyahi et al. noted that additional anticoagulation was associated with less post-thrombotic syndrome (PTS) in BD (13).

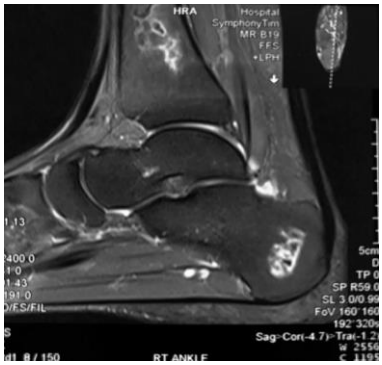

Figure 4. Sagittal T2 fat-suppressed right ankle magnetic resonance imaging (MRI) demonstrates bone infarction in distal shaft of tibia and fibula. Mild edema is seen around the extensor tendons.

Corticosteroids are usually used in association with immunosuppressive agents in patients with BD. Corticosteroid will provide a short period of improvement to initiate a disease-modifying effect of associated drugs. Side effects of corticosteroids are numerous (14). The most common cause of nontraumatic osteonecrosis is corticosteroid consumption.

Avascular necrosis (AVN), also called osteonecrosis, is cellular death (necrosis) of bone components due to interruption of the blood supply. If the AVN involves the bone components of a joint, it usually leads to destruction of the articular surfaces.

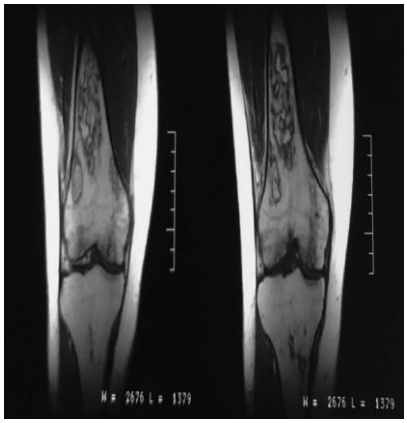

Figure 5. Coronal T1-weighted magnetic resonance imaging (MRI) of right knee demonstrates extensive bone infarction in metaphysis and epiphysis of right knee.

There are many theories about the causes of osteonecrosis. Proposed risk factors include alcoholism, steroid, post-traumatic, caisson disease or decompression sickness (DCS), vascular compression, hypertension (HTN), vasculitis, arterial embolism and thrombosis, radiation, bisphosphonates, sickle cell anemia (SCA), and Gaucher's disease (GD). In some cases, it is idiopathic. Corticosteroid consumption is the most common cause of nontraumatic osteonecrosis, and glucocorticoid-induced osteonecrosis develops in 9-40 percent of patients receiving long-term therapy (15).

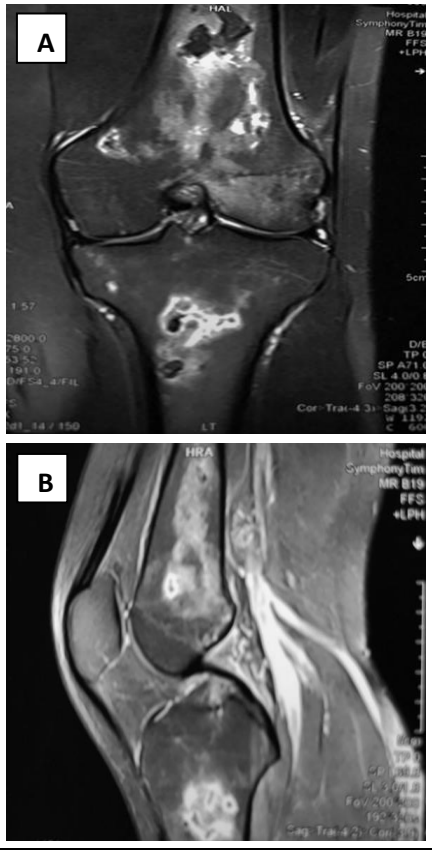

Figure 6. . Coronal fat-suppressed T2-weighted image (A) and sagittal T2-weighted image (B) of left knee show multiple patchy bone infarctions in femur and tibia associated with bone marrow edema.

Some proposed mechanisms for osteonecrosis include endothelial dysfunction, abnormal angiogenesis, and repair mechanisms (4). Multiple mechanisms may occur simultaneously. Kenzora and Glimcher introduced the concept of cumulative stress for the first time (5). Higher frequency of osteonecrosis in some multisystem diseases, such as systemic lupus erythematosus (SLE), compared to other autoimmune diseases, supports the effect of multiple mechanisms on osteonecrosis occurrence (16).

The accumulated cell stress theory suggests that when there are multiple events, the affected bone is unable to recover from chronic stress and osteonecrosis develops. The shortage of procoagulant clearance can lead to progression of osteonecrosis (17). Some studies showed the higher frequency of abnormal coagulant levels in patients with osteonecrosis compared to the normal control group.

Single nucleotide polymorphisms (SNPs) in some genes have been described to be associated with osteonecrosis, such as endothelial NO synthase (eNOS), which has an important role in osteonecrosis development. NO has beneficial effects on skeletal, vascular, and thrombotic events, which have role in osteonecrosis.

However, despite the presence of some important risk factors of AVN in BD, such as endothelial dysfunction, vascular inflammation, vascular thrombosis, and high dose of corticosteroids consumption, interestingly, AVN is very rare in BD and there are just a few case reports in the literature (6-9), which may show the role of genetic factors in osteonecrosis occurrence. Despite the rarity of osteonecrosis in BD, multifocal occurrence of osteonecrosis in our case is considerable.

Conclusion

This article showed that bone infarction should be considered in differential diagnosis of patients with joint pain and without the evidence of arthritis; however, it rarely occurs in patients with BD.

Conflict of Interest

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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