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Atraumatic Osteonecrosis After Estrogen Replacement Therapy Associated with Low Protein S Level in a Patient with Turner Syndrome

Kemal Üreten, MD[1], M. Akif Ozturk, MD[2], Ahmet Bostancı, MD[3], Özcan Çeneli, MD[4], Mustafa Özbek, MD[5], and İbrahim C. Haznedaroğlu, MD[5]

Abstract

Atraumatic osteonecrosis has been associated with a variety of clinical conditions including corticosteroid usage, alcoholism, infections, hyperbaric events, storage disorders, marrow-infiltrating diseases, coagulation defects, and some autoimmune diseases. Osteonecrosis due to thrombophilia is an extremely rare condition with only few cases reported previously in the literature. Hormone-replacement therapies cause increased risk of venous thrombosis, probably by causing a synergistic effect with inherited clotting defects. In this article, we report a young female with Turner syndrome, who developed avascular necrosis of the femoral head during treatment with oral estrogen, which was associated with low protein S levels.

Keywords

osteonecrosis, protein S deficiency, estrogen

Introduction

Osteonecrosis is caused by inadequate blood supply to the affected segment of the subchondral bone. The disease is characterized by an insidious onset without specific clinical symptoms and signs. Atraumatic osteonecrosis has been associated with corticosteroid usage, hyperlipidemia, alcoholism, smoking, infections, endotoxic reactions, hyperbaric events, storage disorders, marrow-infiltrating diseases, coagulation defects, some autoimmune diseases, and hemoglobinopathies (eg, sickle cell disease). Intravascular coagulation appears to constitute the most commonly encountered pathogenetic mechanism through which various unrelated risk factors lead to ischemia and subsequent death of bone and marrow cells, or defective bone repair as the primary event.[1] Thrombophilia defines a variety of acquired and genetic disorders that predisposes to thrombosis. The most common presentations of thrombophilia are deep and superficial venous thrombosis of the lower extremity and pulmonary embolism. Osteonecrosis due to thrombophilia is an extremely rare condition with only few cases reported previously in the literature.[2,3] We herein reported a young female with Turner syndrome who developed avascular necrosis of the femoral head during treatment with oral estrogen, which was associated with low protein S levels.

Case Report

A 38-year-old Turkish woman was referred to our hospital for the evaluation of bilateral hip pain. She was diagnosed with Turner syndrome (45, X0) at age 18. Since then, she was treated with oral estrogen (Premarin 2.5 mg daily) for amenorrhea. Two years ago, she developed bilateral hip pain and was admitted to an orthopedic clinic in another hospital. In that orthopedics clinic, bone scintigraphy was compatible with late

[1] Departments of Rheumatology (KÜ), and Endocrinology (MÖ) Ministry of Health Diskapi Yildirim Beyazit Research and Educational Hospital, Ankara, Turkey
[2] Department of Rheumatology, Gazi University School of Medicine, Ankara, Turkey (MAO)
[3] Department of Gynecology, Ministry of Health Ankara Education and Research Hospital, Ankara, Turkey (AB)
[4] Department of Hematology, Kirikkale University Faculty of Medicine, Kirikkale, Turkey (ÖÇ)
[5] Department of Hematology, Hacettepe University School of Medicine, Ankara, Turkey (İCH)

Corresponding Author:
Kemal Üreten, Turan Güneş Bulvarı, 13 Cad, TunaCantürk sitesi No: 6/6 Oran, Çankaya, Ankara, Turkey
Email: kemalureten@yahoo.com

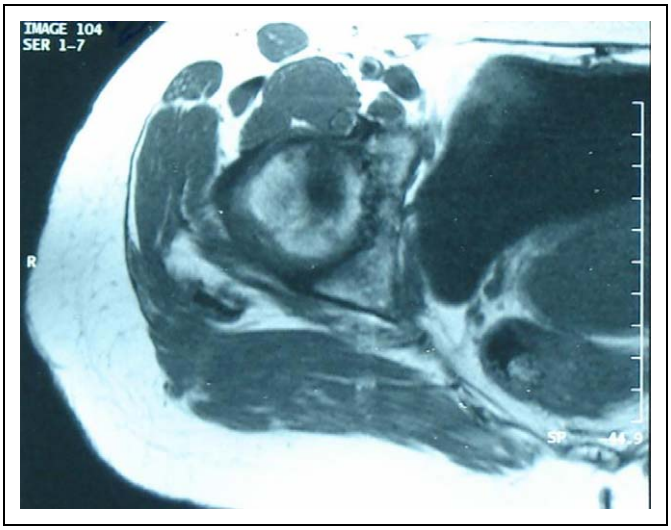

Figure 1. Magnetic resonance imaging (MRI) of the hip, demonstrating narrowing of the coxofemoral joint spaces and degenerative changes; 254 × 190 mm (72 × 72 DPI).

phase aseptic necrosis of bilateral femoral heads. Magnetic resonance imaging (MRI) of the hip demonstrated narrowing in the coxofemoral joint spaces and degenerative changes (Figure 1). However, no further evaluation was made regarding the etiology of aseptic necrosis of the femur head.

The right hip pain worsened in the last month, and she was admitted to our clinic. Physical examination revealed moderate limitation of the left hip joint and severe limitation of the right hip joint. Initial blood count showed a hemoglobin level of 11.5 g/dL, red blood cell count 5.32×10^6/μL, mean corpuscular volume 63.9 fL, white blood cell count 5.100/μL, and platelet count 226.000/μL. Peripheral blood smear showed microcytosis, hypochromia in erythrocytes, normal leukocyte differentials, and normal platelets. The biochemistry profile included serum iron 24 μg/dL (N: 37-145), total iron binding capacity 515 μg/dL (N: 228-428), transferin saturation 5% (N: 15-50), ferritin 3.4 ng/mL (N: 11-307), 25-OH vitamin D 54 nmol/L (N: 20-185), thyrotropin 5.54 uIU/mL (N: 0.35-5.6), free T_3 3.39 pg/mL (N: 2.5-3.9), free T_4 0.91 ng/dL (N: 0.61-1.12), parathormon 35 pg/mL (N: 11-68). Erythrocyte sedimentation rate was 35 mm/h, C-reactive protein 0.31 mg/dL (N: 0-0.8), prothrombin time (PT) 11.9 seconds (N: 11-15 s), international normalized ratio (INR) 1.07 (N: 0.8-1.2), activated partial thromboplastin time (aPTT) 33.5 seconds (N: 22.6-33 s). Antinuclear antibody (ANA), anti–double-stranded DNA (dsDNA) antibody, anticardiolipin antibodies immunoglobulin M (IgM) and G (IgG), antineutrophil cytoplasmic antibodies (ANCA; antimyeloperoxidase and antiproteinase 3) were negative. Homocystein level was 9.79 μmol/L (N: 5.5-17 μmol/L), protein C 95.2% (N: 70%-120%), and protein S 57.3% (N: 70-140%). Factor V Leiden ([FVL] G1691A) mutation and prothrombin (G20210A) mutation were not detected but methylenetetrahydrofolate reductase (*MTHFR*) gene was heterozygously mutated (Table 1). Pelvic x-ray showed bilateral cystic degeneration of femoral head and narrowing in the coxofemoral joint spaces (Figure 2). On bone mineral densitometry, her T and *z* scores were found to be −0.78 and −0.72, respectively. Total hip replacement operation was performed.

Table 1. Laboratory and Radiographic Evaluation of the Patient

International Normalized Ratio	1.07 (N: 0.8-1.2)
Activated partial thromboplastin time	33.5 seconds (N: 22.6-33 s)
Antinuclear antibody	Negative
Anticardiolipin antibodies (immunoglobulin M [IgM], immunoglobulin G [IgG])	Negative
Antineutrophil cytoplasmic antibodies	Negative
Homocystein level	9.79 μmol/L (N: 5.5-17 μmol/L)
Protein C level	95.2% (N: 70-120%)
Protein S level	57.3% (N: 70-140%)
Factor V Leiden (G1691A) mutation	Negative
Prothrombin (G20210A)	Negative
Methylenetetrahydrofolate reductase (*MTHFR*) gene mutation	Heterozygously mutated
Pelvic x-ray	Bilateral cystic degeneration of femoral head and narrowing in the coxofemoral joint spaces
Magnetic resonance imaging	Narrowing in the coxofemoral joint spaces and degenerative changes

Discussion

Osteonecrosis or avascular necrosis of the femoral head (ONFH) is characterized by death of the osteocytes and the bone marrow, which is caused by inadequate blood supply to the affected segment of the subchondral bone. A variety of systemic diseases and clinical conditions are associated with nontraumatic ONFH. These include hypercortisolism, hyperlipidemia, autoimmune diseases, endotoxic reactions, smoking, alcoholism, clotting disturbances, and hypofibrinolysis.[4] Increased tendency for intravascular coagulation is apparently the common pathophysiologic mechanism of those unrelated conditions that lead to ischemia of bone and marrow cells, and eventually to avascular necrosis.[5]

Oral contraceptives and hormone replacement therapies cause a 4-fold increase in the risk of venous thrombosis in participants without any inherited clotting defects such as FVL mutation, antithrombin III, proteins C and S deficiencies. Participants with FVL mutation carry an 8-fold increased risk of thrombosis. However, if those participants with FVL mutation additionally use oral contraceptives, the risk of thrombosis is 30-50 times higher.[6,7] Other inherited coagulation defects, such as a deficiency of protein C, protein S, or antithrombin III, also appear to synergistically increase the risk of venous thrombosis among users of oral contraceptives.[8,9]

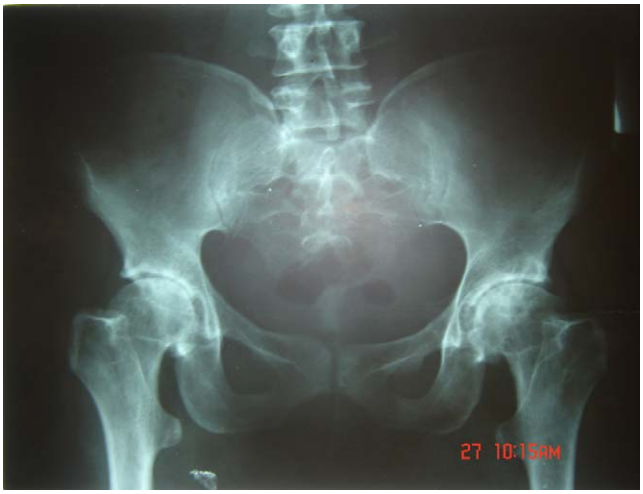

Figure 2. Pelvic x-ray demonstrating bilateral cystic degeneration of femoral head and narrowing in the coxofemoral joint spaces; 812 × 609 mm (72 × 72 DPI).

Protein S is a vitamin K-dependent plasma protein synthesized by the liver. In combination with protein C, it regulates thrombus formation via the inactivating factors Va and VIIIa. Protein S deficiency itself can lead to thrombotic occlusive events in both arterial and venous circulation, including ischemic stroke, deep vein thrombosis, and thromboembolism.[3,10] Exogenous estrogen can further reduce antigenic, functional, and free protein S levels, thus augmenting the thrombophilic state.[11]

Familial protein S deficiency has been shown to cause osteonecrosis of the hip, probably by promoting the formation of venous thrombi in the major veins that drain the head of the femur.[2,12] The resultant increased bone venous pressure and reduction of arterial flow was suggested to produce bone hypoxia and leads to bone death.[2] Moreover, osteonecrosis has been shown to result from estrogen replacement therapy given to patients with underlying thrombophilic protein S deficiency.[3] Our patient was a young female with Turner syndrome, who developed ONFH years after estrogen replacement, without a history of any trauma, rheumatologic disorder, or steroid use. Laboratory evaluation only revealed iron deficiency and low protein S levels. To the best of our knowledge, no association was reported between osteonecrosis and Turner syndrome or iron deficiency. Hence, possible etiologic factors for osteonecrosis in our patient are low protein S levels and estrogen therapy. The protein S level of our patient shows a borderline decrease, which appears to be the result of oral estrogen, not hereditary deficiency.

In summary, we reported a young female who had avascular necrosis of the femoral head during treatment with oral estrogen, probably by lowering the protein S levels. The physicians need to be aware of this rare complication during estrogen replacement in patients who develop symptoms suggesting osteonecrosis.

Declaration of Conflicting Interest

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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