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Letter

Idiopathic avascular necrosis associated with humoral deficiency

The prevalence of avascular necrosis (AVN) of the femoral head is unknown, but estimates indicate that the incidence is between 10,000 and 20,000 new cases a year, with a smaller fraction of those being idiopathic.[1] Idiopathic AVN has been associated with a variety of autoimmune conditions, including systemic lupus erythematosus and antiphospholipid syndrome.[2] It has also been associated with infections and immunodeficiencies, such as human immunodeficiency virus (HIV).[3] It has never been described in association with a functional humoral deficiency.

A 47-year-old man presented for an immunologic evaluation of bilateral idiopathic femoral head AVN. His medical history was significant for shingles at 23 years of age, mild intermittent asthma (without current or past steroid use), contact dermatitis (remote minimal topical steroid use), migraines, and gastroesophageal reflux disease. He presented with severe, acute, right-sided, sharp, nonradiating hip pain, which resolved. He was eventually unable to walk after the second reoccurrence of the hip pain. His pain remained isolated to the right side. He had no history of trauma to the hip area. His medications at the time included zolpidem tartrate, omeprazole, rizatriptan, tramadol, diazepam, and armodafinil. Radiography revealed a shattered right-sided femoral head. Magnetic resonance imaging revealed bilateral AVN of the femoral head (Fig 1). Arthrocentesis revealed no evidence of infection (acid-fast bacilli, bacterial, and fungal culture results were negative). He had no history of smoking or drug use, and he used alcohol occasionally. His laboratory evaluation revealed a normal complete blood cell count, completely normal comprehensive metabolic profile, and normal lipid panel. Serologic test results for VDRL, HIV, anti—double-stranded DNA, rheumatoid factor, and anticardiolipin antibodies were negative. There was no evidence for clonality or malignant tumor based on a normal serum protein and urine protein electrophoresis and flow cytometry results. The lymphocyte subset evaluation revealed the following normal results: CD3, 71% (880 cells/μL); CD4, 46% (570 cells/μL); CD8, 31% (384 cells/μL); CD19, 10% (124 cells/μL); and CD56, 13% (161 cells/μL). Mitogen stimulation evaluations were all within the normal range in response to phytohemagglutinin, Concavalin A, and pokeweed. The patient had a normal response to antigen stimulation to *Candida* and tetanus. He was found to have normal serum IgA levels (124 mg/dL), normal serum IgM levels (137 mg/dL), and normal serum IgG levels (916 mg/dL) but did have IgG2 (227 mg/dL) and IgG3 (21mg/dL) subclass deficiencies. He had a normal antibody response to tetanus. He had poor to absent response to nonconjugate and conjugated pneumococcal polysaccharide vaccines (Table 1).

AVN is known to have a variety of causes; however, its pathogenesis remains controversial. It is thought to be a combination of genetic, metabolic, and vascular factors that lead to dysfunction of

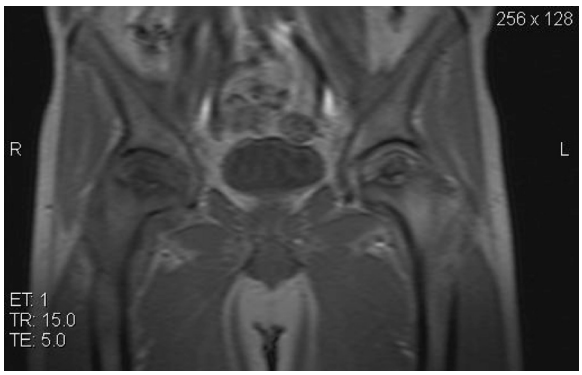


Figure 1. Magnetic resonance image showing bilateral femoral head avascular necrosis.

circulation within the bone, thus resulting in hyperemia, demineralization of the bone, and finally collapse.[4]

More than 80% of the cases that are nontraumatic are indeed associated with heavy alcohol use and glucocorticoid intake.[1] Mont et al[5] found that corticosteroid and alcohol-associated osteonecrosis have been associated with lipopolysaccharide interactions that stimulate Toll-like receptor 4 signaling. The signaling activates proinflammatory pathways and alters secretion of interleukin (IL) 23, IL-1, transforming growth factor β, IL-10, and tumor necrosis factor α and may be linked to the pathogenesis of AVN.[5] The remaining cases have been associated with HIV, sickle cell disease, inherited thrombophilia, Gaucher disease, and autoimmune or immune dysfunction. The latter include systemic lupus erythematosus and antiphospholipid antibody syndrome (APS).

APS illustrates one example of the association between AVN and the humoral immune system. APS is a thrombophilic disorder that is characterized by arterial or venous thrombosis and at least 1 positive laboratory criterion, namely, the presence of 1 or more of the antiphospholipid antibodies on 2 or more occasions at least 12 weeks apart.[6] AVN has been well described in patients who have antiphospholipid antibodies, primarily in patients who have also been diagnosed with systemic lupus erythematosus and who therefore have been exposed to glucocorticoids. However, there have been multiple case reports of an association between primary antiphospholipid antibody syndrome and AVN that could not otherwise be explained by other major risk factors.[7,8] The mechanism of this association is poorly understood, but there is some thought that antiphospholipid antibodies have effects on the endothelium and platelets and possibly on neural tissues and hormonal and complement pathways,[9] thereby leading to AVN.

HIV has also been associated with idiopathic AVN. Mehta et al[10] reviewed magnetic resonance imaging reports in HIV-positive

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Table 1
Streptococcus pneumoniae Titers Before and After Conjugated Vaccine

S pneumoniae serotype	Level before vaccine, μg/mL	Level after pneumovax vaccine, μg/mL	Level after prevnar vaccine, μg/mL
1	6.3	13.2	13.9
3	0.4	0.9	1.0
4	<0.3	0.5	0.5
5	2.5	3.9	4.5
8	1.9	3.0	3.4
9	0.4	1.3	1.0
12	0.6	0.9	0.9
14	1.2	1.3	1.3
19	0.8	1.0	0.9
23	0.6	0.7	0.7
26	1.2	1.6	1.8
51	0.5	0.9	0.9
56	1.5	2.1	2.7
68	0.6	1.4	1.2

patients at a tertiary referral HIV center, identifying 22 patients with AVN and reviewing known risk factors for AVN. Seventy-three percent of patients had more than 2 risk factors, including highly active antiretroviral therapy (91%), protease inhibitors (68%), hypercholesterolemia (59%), corticosteroid use (55%), hypertriglyceridemia (45%), smoking (45%), alcohol use (27%), and CD4 count less than 200 cells/μL (23%). Nine percent were idiopathic.[10] This finding may suggest that there are aspects of immunologic depression that predispose patients with HIV to develop AVN.

The association among APS, HIV, and AVN has been well described[2,3,7–10] and suggests that dysregulation of the immune system can be associated with AVN. However, this association has never been shown with any functional humoral deficiencies. We describe the first case of an association between a functional humoral deficiency and AVN. Further research is needed to clarify the mechanism that predisposes patients with immune dysregulation conditions to develop idiopathic AVN.

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