Avascular Necrosis of Bone in Patients with Human Immunodeficiency Virus Infection: Report of 6 Cases and Review of the Literature

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In 1998 and 1999, we diagnosed avascular necrosis of bone in 6 patients in our human immunodeficiency virus clinic practice, an incidence of 0.45%, which is 45 times greater than would be expected in the general population. Antiphospholipid antibodies and hyperlipidemia secondary to protease inhibitor therapy have been implicated as possible etiologies; however, these abnormalities cannot explain all cases of avascular necrosis of bone reported in patients with human immunodeficiency virus infection.

Over the past decade, there have been many case reports of avascular necrosis of bone (AVN) occurring in persons with underlying HIV infection [1–12]. Most of these patients appear to have no known predisposing factor for AVN, and it has been suggested that HIV infection itself may be a risk factor for osteonecrosis. Belmonte et al. [4] described 3 HIV-infected persons with AVN who had positive test results for antiphospholipid antibodies and suggested a possible association between the presence of antiphospholipid antibodies and osteonecrosis in persons with HIV disease, as has been shown in patients with systemic lupus erythematosus.

Recently, it has been suggested that protease inhibitor therapy may be responsible for cases of osteonecrosis in HIV-infected persons with no other known risk factor for AVN, perhaps because of the resulting hyperlipidemia, specifically hypertriglyceridemia, a known risk factor for AVN [11, 13, 14]. Two recent abstracts have presented results of cross-sectional studies of bone mineral density in HIV-infected persons who were receiving highly active antiretroviral therapy (HAART) that includes protease inhibitors [15, 16]. Osteoporosis occurred in 10%–21% of patients who were receiving protease inhibitors. Neither study examined HIV-infected patients who were not receiving antiretroviral therapy. Although the pathogenesis of AVN is unrelated to that of osteoporosis, these reports have fueled speculation that protease inhibitor therapy may have effects on bone metabolism. It is unlikely that protease inhibitor therapy is the only explanation for a possible increased risk for AVN, because case reports first began to appear in the literature before the availability of these agents. A remarkable feature of many of the cases of AVN in association with HIV infection that have been reported to date has been the presence of osteonecrosis at multiple sites. In fact, one report [2] suggested that the presence of unexplained multiple-site AVN should prompt consideration of HIV testing.

During the past 2 years, we have diagnosed AVN in 6 patients in our HIV clinic practice. Four of our patients have AVN at >1 site. The incidence of AVN in our clinic population over the last 2 years is 0.45%, ~45 times greater than would be expected in the general population; however, 3 patients had a definite predisposing factor for AVN (long-term corticosteroid therapy in 2 and a history of heavy ethanol use in 1). We report the clinical characteristics of these patients and review 31 additional reported cases of AVN associated with underlying HIV disease.

Case reports. The HIV/AIDS clinic at Wayne State University School of Medicine provides care for ~1300 persons in the following risk groups: male-male sexual activity, 40%; injection drug abuse, 21%; male-female sexual activity, 32%; and hemophilia, 2%. Thirty percent of our patients are female. Forty-one percent of our patients have had an AIDS indicator condition and/or a CD4 cell count <200 cells/mm^3. Clinical characteristics of the 6 patients with AVN and underlying HIV infection are summarized in table 1 and described briefly below. No cases of AVN were diagnosed in our clinic before those reported here.

Patient 1, a 47-year-old man, received a diagnosis of AVN of both hips in January 1999 and of bilateral AVN of the shoulders in September 1999. The patient's history was remarkable for CNS toxoplasmosis, esophagitis due to *Candida* species, colitis due to cytomegalovirus, and Kaposi's sarcoma of the gastrointestinal tract. At the time of diagnosis of AVN, his CD4 cell count was 420 cells/mm^3 and his viral load was 600 copies/mL. His nadir CD4 cell count was 27 cells/mm^3. The patient had received HAART (including a protease inhibitor) for ~2 years. Serum triglyceride levels, measured ~8 months after the

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Table 1. Clinical characteristics of patients with avascular necrosis of bone (AVN) associated with HIV infection.

Reference	Year	Age, y	Sex	Risk factor for HIV infection	CD4 cell count, cells/mm^3	HIV load, copies/mL	Site of AVN	Possible risk factors for AVN			
								Serum triglyceride levels	Result of test for antiphospholipid antibodies	PI use	Other
Present	2001	47	M	MSM	420	600	Bilateral hips and shoulders	Elevated	NR	Yes	
		44	M	MSM	700	<200	Bilateral hips	Normal	Positive	Yes	Prednisone therapy for 8 months for Crohn's disease
		49	F	M-F	165	225,000	Left hip	Normal	Positive	Yes	Ethanol abuse
		33	M	MSM	0	325,000	Left hip	Normal	Negative	Yes	
		34	M	M-F	468	30	Bilateral hips	Normal	NR	Yes	Prednisone therapy for >4 years for thrombotic thrombocytopenic purpura
		38	F	M-F	663	20,000	Bilateral hips	Normal	Positive	No	
[1]	1990	34	M	NR	200	NR	Right hip	NR	NR	No	
[2]	1991	28	F	M-F	113	NR	Bilateral hips, shoulders, and knees	Normal	Negative	No	
		20	M	MSM	510	NR	Bilateral hips and shoulders	Normal	Negative	No	
[3]	1993	26	M	IDA	250	NR	Left hip	Elevated	NR	No	
		27	M	IDA	960	NR	Bilateral hips	NR	Positive	No	
[4]	1993	23	F	IDA	600	NR	Bilateral knees and proximal tibias	Normal	Positive	No	
		26	M	IDA	900	NR	Bilateral hips	Normal	Positive	No	
		31	M	IDA	450	NR	Bilateral hips	Elevated	Positive	No	

[5]	1995	38	M	NR	NR	NR	Bilateral hips	NR	NR	No	
		43	M	NR	NR	NR	Right hip	NR	NR	No	
		43	M	NR	NR	NR	Right hip	NR	NR	No	
		36	F	NR	NR	NR	Bilateral hips	NR	NR	No	
[6]	1995	45	M	IDA	276	NR	Left knee	Elevated	Negative	NR	
[7]	1995	32	M	MSM	1064	NR	Bilateral knees	NR	Positive	NR	Long-term prednisone therapy for systemic lupus erythematosus
		55	F	M-F	299	NR	Right hip	NR	Negative	NR	Long-term prednisone therapy for systemic lupus erythematosus
[8]	1997	25	M	MSM, IDA	NR	NR	Left knee	NR	NR	NR	
		36	M	MSM	NR	NR	Left hip, bilateral knees	NR	NR	NR	
		28	F	NR	NR	NR	Left hip	NR	NR	No	
		30	F	IDA	NR	NR	Right hip	NR	NR	No	
		29	M	MSM	NR	NR	Bilateral hips	NR	NR	No	
		46	M	MSM	NR	NR	Bilateral hips	NR	NR	NR	
[9]	1998	35	F	IDA	NR	NR	Left hip	NR	Positive	NR	
		41	M	M-F	NR	NR	Right hip	NR	NR	NR	
		34	M	MSM	NR	NR	Left hip	NR	Positive	NR	
		31	M	IDA	NR	NR	Bilateral hips	NR	Positive	NR	
[10]	1998	33	M	IDA	NR	NR	Bilateral knees	NR	Negative	NR	
[11]	1999	32	F	NR	980	<50	Bilateral hips	Elevated	NR	Yes	
		48	M	NR	350	<50	Bilateral hips and proximal tibias	Elevated	NR	Yes	
[12]	1999	30	M	MSM	364	896	Left distal femur	NR	Negative	No	
		35	M	MSM	57	684,184	Bilateral hips	NR	Negative	Yes	
		38	M	MSM	794	NR	Left talus	NR	Negative	No	

NOTE. F, female; M-F, male-female sexual activity; IDA, injection drug abuse; M, male; MSM, men who have sex with men; NR, not reported; PI, protease inhibitor.

diagnosis of AVN, were mildly elevated at 199 mg/dL (normal range, 35–160 mg/dL). Two years before the diagnosis of AVN, the patient had received steroid therapy (dexamethasone) for ~1 month for CNS toxoplasmosis. He underwent total right hip arthroplasty in October 1999 with good results.

Patient 2, a 44-year-old man, received a diagnosis of AVN of both hips in April 1999. His CD4 cell count at the time of diagnosis was 700 cells/mm^3 (nadir, 154 cells/mm^3), and his viral load was <200 copies/mL. His history was remarkable for Crohn's disease, which was diagnosed ~8 months before the diagnosis of AVN and for which he was taking prednisone. His HIV treatment history included the use of several protease inhibitors. Serum triglyceride levels were mildly elevated (229 mg/dL) the year before the diagnosis of AVN but were within the normal range on a subsequent measurement in September 1999, even though he continued to receive a regimen that included a protease inhibitor. A screen for antiphospholipid antibodies yielded positive results.

Patient 3, a 49-year-old woman, received a diagnosis of AVN of the left hip in June 1999. Her CD4 cell count and viral load were 165 cells/mm^3 and 225,000 copies/mL, respectively (nadir CD4 cell count, unknown). The patient reported a history of heavy ethanol use for many years. HIV treatment included a protease inhibitor for the past 2 years. There was no history of any other predisposing factor for osteonecrosis. Serum triglyceride levels were normal, and a screen for antiphospholipid antibodies yielded positive results.

Patient 4, a 33-year-old man, received a diagnosis of AVN of the left femoral head in July 1998. His CD4 cell count at the time of diagnosis was 0 cells/mm^3 and his viral load was 325,000 copies/mL. He had taken antiretroviral therapy (which included protease inhibitors) in the past but had refused therapy for >1 year before the diagnosis of AVN. At the time that AVN was diagnosed, his serum triglyceride levels were in the normal range and a screen for antiphospholipid antibodies was negative.

Patient 5, a 34-year-old man, received a diagnosis of AVN of both hips in August 1999. His CD4 cell count at the time of diagnosis was 468 cells/mm^3 (nadir, 228 cells/mm^3), and his viral load was 30 copies/mL. His history was remarkable for thrombotic thrombocytopenic purpura, for which he had taken prednisone for >4 years. HIV treatment included protease inhibitor therapy. Serum triglyceride levels were normal when they were measured in May of 1999 and elevated (325 mg/dL) when they were measured in September of 1999.

Patient 6, a 38-year-old woman, received a diagnosis of AVN of both hips in November 1999. At the time of diagnosis, her CD4 cell count was 663 cells/mm^3 (nadir, 420 cells/mm^3), and her viral load was 20,000 copies/mL. The patient's history was remarkable for an episode of severe lactic acidosis and acute pancreatitis, attributed to stavudine therapy, in August of 1998. The patient recovered completely from this episode and had no clinical evidence of chronic pancreatitis. Serum triglyceride levels were measured on several occasions before the diagnosis of AVN and were normal; a screen for antiphospholipid antibodies yielded positive results. The patient had never received protease inhibitor therapy. She underwent total left hip arthroplasty in April of 2000 with good results.

Literature review. The MEDLINE database was searched for published case reports of AVN in patients with HIV infection in the English-language literature published from January 1963 through January 2000. References of case reports and pertinent review articles were reviewed to find additional cases.

Thirty-one cases of AVN in persons with underlying HIV infection have been published (table 1). A review of these case patients, in addition to our 6, reveals that the mean age at the time of AVN diagnosis was 35.4 years (range, 20–55 years). Ten patients were women. The risk factor for HIV acquisition was reported for 29 of the 37 patients: men who had sex with men, 45%; injection drug abusers, 34%; and male-female sexual activity, 21%. The CD4 cell count at the time of AVN diagnosis was reported for 22 of the 37 patients. The mean CD4 cell count was 481 cells/mm^3 (range, 0–1064 cells/mm^3). The hip was the most common site of involvement, followed by the knee and then the shoulder. Osteonecrosis of ⩾2 sites occurred in 21 (57%) of 37 patients, most commonly in both hips. Involvement of 4 sites occurred in 4 patients, most commonly both hips and shoulders. A known risk factor for AVN was reported in 5 of the 37 patients: long-term prednisone therapy for 4 and a history of heavy ethanol use for 1. If patients with elevated serum triglyceride levels are included, a risk factor for AVN was present in 11 (30%) of 37 patients, although data on serum triglyceride levels were not reported for the majority of case patients (22).

A review of the cases published in 1995 and beyond, when protease inhibitor therapy became common, revealed that data on HIV treatment were available for 18 of 29 patients, 8 of whom received protease inhibitor therapy. Data on serum triglyceride levels were reported for 7 of these 8 patients, and 3 had elevated levels. Data regarding antiphospholipid antibody measurements were available for 20 patients, 11 of whom were found to have antiphospholipid antibodies.

Discussion. We have observed that the incidence of AVN in our HIV clinic population over the past 2 years is greater than would be expected in the general population. Case reports of osteonecrosis occurring in persons with HIV infection have appeared in the literature since 1990. At present, the available data are insufficient to conclude that the incidence of AVN in HIV-infected persons is increased, and large epidemiologic studies are needed. It has been suggested that the apparent increased incidence of AVN in this population may be caused by an increased prevalence of predisposing factors for osteonecrosis, including hypertriglyceridemia, corticosteroid use,

and ethanol abuse [17]. For many of the case patients described to date, however, no apparent risk factor for AVN could be determined, although many case reports lack complete data, such as serum triglyceride measurements.

On the basis of our literature review, it appears that AVN occurs in all known HIV risk groups. The mean CD4 cell count at the time of diagnosis was high (481 cells/mm^3); however, several cases were reported in persons with very low CD4 cell counts. Data regarding viral load were available for only a small number of patients (10), but it appears that osteonecrosis may occur in patients with suppressed viral replication as well as in those with high viral loads.

Multiple-site osteonecrosis was seen commonly in these patients, strongly suggesting that a systemic process may be the underlying pathogenesis. Several recent reports have suggested a possible link between AVN and the use of protease inhibitors, perhaps as a result of hyperlipidemia induced by protease inhibitors [11, 13, 14]. Protease inhibitor use cannot be the only factor, however, because case reports began to appear before 1995, the time when these agents became widely available, and fewer than one-half of the patients in our review whose treatment history was reported were exposed to these drugs. Hypertriglyceridemia, independent of protease inhibitor therapy, has previously been reported in a high proportion of HIV-infected patients, perhaps because cytokines are produced in response to chronic infection [18]. Data on serum triglyceride measurements were available for fewer than one-half of the patients described here. However, of the 15 patients for whom data were available, only 6 had elevated triglyceride levels.

Corticosteroids are used in the management of a number of HIV-related conditions, but the dose and duration of therapy for most indications, such as the short course of dexamethasone for CNS toxoplasmosis in our first patient, should not pose a risk for AVN. Although there are case reports of AVN linked to short-course corticosteroid therapy [19, 20], it is unknown whether short courses of steroid therapy truly pose a risk for AVN [21]. Some patients may require long-term corticosteroid therapy, however, and long-term prednisone use was the likely risk factor for AVN in 2 of our patients, as well as 2 additional patients reported in the literature.

Belmonte et al. [4] have suggested a possible association between the presence of antiphospholipid antibodies and AVN in persons with HIV infection. These antibodies have been reported in a high proportion of persons with HIV infection [22]. Antiphospholipid antibodies have been implicated in the pathogenesis of AVN in patients with systemic lupus erythematosus, and the potential role of such antibodies in the pathogenesis of osteonecrosis in patients with HIV disease deserves further study.

The most frequently advocated management for advanced osteonecrosis of the knee or hip is prosthetic replacement. To date, 2 of our patients have undergone total hip arthroplasty; analgesics, ambulation assist devices, and physical therapy are currently being used to manage to conditions of the other 4 patients. All have been referred for orthopedic consultation.

In summary, osteonecrosis may occur at a higher-than-expected frequency in persons with underlying HIV infection and can occur at any level of immunosuppression. Musculoskeletal pain is common in persons with HIV infection, and clinicians should be aware of the possible association between AVN and HIV infection and maintain a high index of suspicion for AVN in HIV-infected patients with unexplained bone pain. An association of AVN with hypertriglyceridemia due to protease inhibitor therapy has been postulated, but review of the available data suggests that this clearly is not the only explanation for osteonecrosis in patients with HIV. It is likely that the etiopathogenesis of AVN in HIV is multifactorial, and further study of the role of antiphospholipid antibodies, as well as a better understanding of all of the metabolic complications of HAART, is needed.

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