Avascular Necrosis and Protease Inhibitors

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Avascular necrosis (AVN) indicates ischemic death of the bone due to insufficient arterial blood supply. The incidence rate of AVN is higher in HIV-infected patients than in the general population. Although the exact etiology of AVN remains unclear, the literature has shown a relationship between AVN and exposure to highly active antiretroviral therapy (HAART). It should be noted, however, that AVN has been reported before the era of HAART, thus suggesting the involvement of other causative factors as well. Three case reports based on patients attending the infectious disease clinic are presented. No cases of AVN are reported in our clinic population prior to this report. Affected sites of AVN included the hip and shoulders. The incidence of AVN within our patient population was higher than the general population.

Although the introduction of HAART has improved patient longevity, it has also led to longer exposure to antiretroviral (ARV) therapy. Thus, it is likely that treatment-related complications may become more apparent in the HIV-infected population. This may be the case with AVN. Therefore, clinicians need to be alert to the potential complication of AVN in HIV-infected patients treated with HAART.

Key words: protease inhibitor therapy ■ HIV/AIDS ■ avascular necrosis

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INTRODUCTION

Avascular necrosis (AVN), also termed osteonecrosis, indicates ischemic death of the bone as a result of insufficient arterial blood supply.[1-3] The incidence rate of AVN has been reported to be 0.135% in the general population, although incidence rates ranging 0.3–0.45% have been observed in HIV-infected patients.[1-3] Although the exact etiology of osteonecrosis remains unclear, predisposing factors, such as HIV-related complications, an adverse event of highly active antiretroviral therapy (HAART) or a result of a HIV-associated disease, have been suggested.[4] Additional factors associated with AVN have included corticosteroid use, alcoholism, intravenous drug use, smoking, antiphospholipid antibodies, hyperlipidemia, sickle cell anemia, radiation exposure and systemic lupus erythematosus.[3,6] Metabolic factors, such as hyperlipidemia, have also been strongly associated with use of protease inhibitors.[7] Regardless of the etiology, AVN has become an emerging manifestation within the HIV population.

Three case reports based on patients attending the ambulatory infectious disease clinic at Howard University Hospital between January 2000 and December 2000 are presented. We are not aware of any reported cases of AVN in our clinic population prior to these reported cases. Demographic and clinical information of all patients (n=160) seen in the clinic between January and December 2000 are summarized in Table 1. Risk factors common to the three reported cases include use of protease inhibitors and alcohol abuse (Table 2). Affected sites of AVN included the hip and shoulders (Table 2). The incidence of AVN within our patient population was 1.9% as compared to 0.135% in the general population.[1] Our incidence rate is also higher than other reported rates of AVN in HIV patients.[1-3] Detailed information on three cases of AVN noted in our patient population is described below. It should be noted that the testosterone levels and HIV genotypes were not available.

Case Report 1

A 58-year-old male with HIV diagnosed in 1987 presented to the infectious disease clinic on February 8, 1997 for management of HIV. The CD_4 count at that time was 146 cells/mm^3. The patient was started on lamivudine, stavudine and indinavir. His past medical history was significant for myocardial infarction in 1981, hypertension, schizophrenia and Parkinsonism. The patient denied alcohol usage but admitted to smoking one pack a day for the past five years and smoking marijuana. In June 1997, the patient complained of flank pain. Indinavir was discontinued from the regimen and replaced with nelfinavir. In December 1997, the patient complained of low-back pain, which was resolved with analgesics. The patient continued the same regimen and, in March 2000, he presented to the clinic complaining of bilateral hip pain and pain in his groin. A hip x-ray showed AVN (Figure 1). His CD_4 count at that time was 572 cells/mm^3, and HIV RNA was undetectable (<400 copies/mL). He was referred to orthopedic surgery for hip replacement.

Case Report 2

A 47-year-old male with HIV diagnosed in 1991 and hypertension presented to the infectious disease clinic in July 1999 for management of HIV. At the time of presentation, his CD_4 count was 82 cells/mm^3, and HIV RNA was 126,420 copies/mL. He was on ritonavir and zalcitabine for more than one year but was noncompliant with medications. The patient denied history of smoking or alcohol but admitted intravenous drug usage for 10 years prior to 1997. There was no history of dyslipidemia or steroid use in the past. In January 2000, his medications were changed to efavirenz, stavudine and nelfinavir. In March 2000, he presented to the clinic with pain in the hips, knees and shoulders. Physical examination at that time was unremarkable. After being evaluated by rheumatology and neurology, he was managed with analgesics for peripheral neuropathy. In May 2000, he was admitted to the hospital with left hip pain for three days, which was progressively getting worse, aggravated by movement and somewhat relieved by analgesics. The patient

Table 1. Characteristics of HIV patients

Patient Characteristics	Patient Numbers	% (N=160)
Gender		
Male	111	69.4%
Female	49	30.6%
Race		
African-American	153	95.6%
Age		
>50 years	52	32.5%
AIDS	75	46.9%
On protease inhibitors	90	56.3%
HIV Viral Load		
<400 copies/mL	47	(29.4%)
>750,000 copies/mL	11	(6.9%)
CD_4	Mean 318 cells/mm^3	

Table 2. Clinical Characteristics of HIV-Infected Patients with AVN

Patient #	Age	Sex	Risk Factor HIV	CD4 (cells/mm^3)	Viral Load (copies/mL)	Initiation of PI Therapy	Date of AVN Diagnosis	AVN Site	Predisposing Factors for AVN
1	58	M	NR	572	<400	1997	2000	Hips	PI use
2	47	M	IVDA	97	<400	1999	2000	Bilateral shoulders	PI use, megestrol
3	53	M	MSM	154	96,712	1997^	2000	Hips	PI use

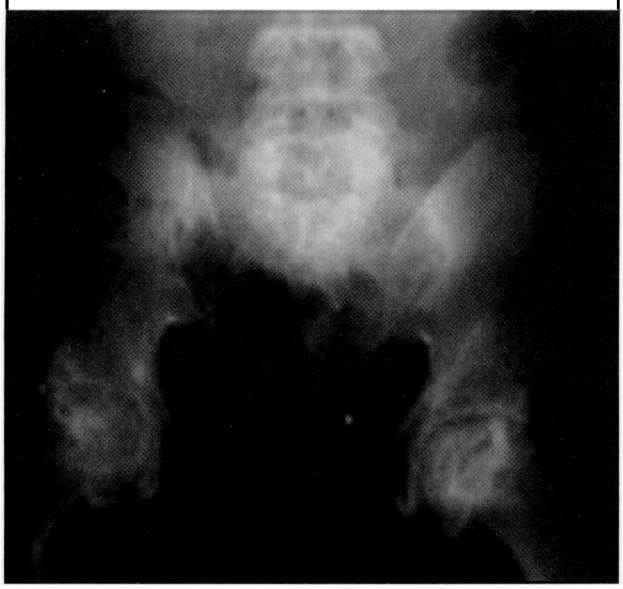
^ From 1994–1997, patient did not receive protease inhibitor therapy; NR: not reported; IVDA: intravenous drug abuse; MSM: Men having sex with men; PI: protease inhibitor

denied any history of trauma or fall. A pelvic x-ray revealed fracture of the left femoral neck with superior displacement of distal fragment. He underwent left hip hemiarthroplasty and was discharged home after rehabilitation. During his follow-up visit to the clinic in August 2000, the patient complained of pain in both shoulders. His CD_4 count at that time was 97 cells/mm^3, and HIV RNA was undetectable (<400 copies/mL). Physical examination was significant for restricted movements and tenderness over both shoulders. An x-ray of the shoulders was negative. An MRI revealed AVN of both shoulders. He underwent bilateral shoulder hemiarthroplasty in October 2000.

Case Report 3

A 53-year-old male with HIV diagnosed in 1987 presented to the clinic in 1994 for management of HIV. During his initial visit, his CD_4 count was 50 cells/mm^3, and he was on zidovudine, zalcitabine and sulfamethoxazole/trimethoprim. He admitted to a history of alcohol use in the past and that he smoked one pack a day for past five years, but he denied any history of drug use. There was no history of dyslipidemia or steroid use in the past. His regimen was changed to lamivudine and stavudine, which resulted in improvement of CD_4 count and viral load. In 1997, his regimen was again changed to nevirapine, indinavir and lamivudine due to declining CD_4 counts. In August 1999, he complained of back pain, which resolved with analgesics. In February 2000, he complained of back pain radiating to the groin and aggravated with movement. The CD_4 count at that time was 154 cells/mm^3, and HIV RNA was 96,712 copies/mL.

Figure 1. Hip x-ray showing avascular necrosis



Several x-rays of the hip showed AVN of the femoral head. The patient was referred to orthopedic surgery for hip replacement.

DISCUSSION

The development of AVN of the bone continues to be more frequent among HIV-positive patients.[1-9] A retrospective chart review conducted from 19 HIV clinics in Spain reported 23 cases of AVN over a 10-year period with a notable increase in frequency of AVN from 1.6 per 1,000 AIDS patients during 1993–1996 to 14 per 1,000 patients during 1997–2000.[5] The authors also found that of the 23 reported cases of AVN, 91% had exposure to antiretroviral (ARV) therapy. Five reports on AVN have most often involved the femoral head and the hip; however, multiple sites may be affected.[5-9] There are reports suggesting an association between protease inhibitors and a decreased bone density in patients.[7-9] Although it should be noted that AVN was reported before the era of ARV therapy, evidence suggesting HIV virus as the only risk factor for the development of avascular necrsosis is limited.[7,8] For example, one study reported 33 cases of osteonecrosis, but only 33% of the cases were identified as having the HIV virus as the sole risk factor the development of osteonecrosis.[8] However, there is literature suggesting that the etiology of AVN may include multiple risk factors.[1,8] In their report of seven cases, Valencia and colleagues found the etiology of AVN to be multifactorial, including alcohol abuse, hypertrigylceridemia, corticosteroid use and protease inhibitor-containing regimens.[1] In some of the reported cases, although the average CD_4 count was 501cell/mm^3 and the HIV RNA was suppressed (<50 cell/mm^3), many patients still developed AVN.[1]

CONCLUSION

The introduction of HAART emerged to improve patients' longevity. However, this will mean longer duration of exposure to ARV therapy. As a consequence it is likely that treatment-related complications will become more apparent in the infected population. This is currently the case with AVN. Therefore, clinicians need to be alert to the subtle yet frequent complication of AVN in patients on ARV therapy, especially those patients on protease inhibitors.

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