

Perspective

Bone Disorders, Hypertension, and Mitochondrial Toxicity in HIV Disease

Osteonecrosis, osteopenia and osteoporosis, hypertension, and mitochondrial toxicity are among the medical conditions observed in patients with HIV disease. In some cases, these disorders have been associated with antiretroviral therapy or particular antiretroviral agents. In other cases, their etiology remains unclear. Meg D. Newman, MD, discussed data from studies of these conditions and current management approaches at the Clinical Pathway of the Ryan White CARE Act 2002 All Grantee Conference held in Washington, DC, in August 2002.

Case 1: Osteonecrosis

Case Presentation

In 1996, a male patient who is currently 33 years old was in hospice care, with a CD4+ cell count of 1/μL, AIDS dementia complex, bilateral cytomegalovirus retinitis, Kaposi's sarcoma of the extremities, and recurrent bacterial infections. After several years of potent antiretroviral therapy, the patient's condition is much improved. In 2001, he presents with viral load below the assay detection limit and a CD4+ cell count of 480/μL. He is still blind in one eye, but is living independently and working part time. He describes new bilateral hip pain, worse in the right hip than in the left hip, and has no history of recent or remote trauma. Examination shows decreased internal rotation of the hips, with more significant findings for the right hip. Plain radiographs of both hips are unremarkable. Magnetic resonance imaging (MRI) with gadolinium shows bilateral osteonecrosis.

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Discussion

Hip osteonecrosis in an HIV-infected patient was first reported in 1990, well before the advent of potent antiretroviral therapy. Subsequent reports of hip and multiple joint osteonecrosis were published in 1991 and 1993. Osteonecrosis may result from direct or indirect damage; sources of indirect damage include corticosteroid use, alcohol abuse, cigarette smoking, sickle cell anemia, coagulopathies, lupus, hyperlipidemia, and chronic pancreatitis. HIV infection may constitute a risk factor. Although protease inhibitor (PI) use has been broadly discussed as being associated with osteonecrosis, there is scant evidence of a direct causal effect.

The site of osteonecrosis is the subchondral bone located beneath the articular surface. The vascular supply to subchondral bone starts with arterioles and proceeds to sinusoids that turn at 180 degrees and exit as venules. Blood flow is slow and tortuous, making subchondral bone susceptible to microemboli, vasospasm, and increased intraosseous pressure that can occlude the bone. The femoral head is the most common site of osteonecrosis. In the case of corticosteroid use and chronic alcohol abuse, postulated mechanisms of injury consist of altered fat metabolism resulting in fatty liver or hyperlipidemia, with deposition of fat emboli. In addition, there may be increased intraosseous lipocytes in the marrow, resulting in increased intraosseous pressure with loss of small capillaries and subsequent ischemia. Individuals who smoke cigarettes are at 4-fold greater risk of osteonecrosis, which is probably associated with vasospasm. Ischemia leading to bone necrosis may be protracted or sudden. Death of osteocytes stimulates production of undifferentiated mesenchymal cells into the necrotic cancellous bone.

Some of these develop into osteoblasts, but bone resorption is ongoing and is ultimately more efficient. The result is that subchondral bone cannot adequately support the joint, and microfractures and collapse of the bone ensue.

A key point in the evaluation for osteonecrosis is never to rely on plain radiographs to rule out the disorder. In addition, early disease is difficult to detect on plain radiographs. MRI should be used instead, since it has a sensitivity of approximately 90% in detecting osteonecrosis. Bilateral hip imaging should be performed, since bilateral disease is present in approximately 40% of cases.

In a recently reported study by Miller and colleagues (*Ann Intern Med*, 2002), MRI revealed evidence of osteonecrosis in 15 (4.4%) of 339 asymptomatic HIV-infected patients and none of 118 HIV-uninfected patients. Six patients had bilateral disease. All lesions had typical features of osteonecrosis with diminished signal on T1-weighted images and bright signal on fat-suppressed T2-weighted images. Most patients had band- or ring-shaped lesions. Three of the 9 patients with unilateral disease had wedge-shaped lesions in the anteromedial aspect of the femoral head and 2 had small subchondral lesions in the anterior superior aspect of the femoral head. All patients with osteonecrosis had negative plain radiographs. On physical examination, 14 patients with osteonecrosis had abnormal findings, with 11 having abnormal range of motion; however, abnormalities were also found in patients without osteonecrosis in the same population. At the time of publication of these findings, 10 patients had reported some hip discomfort, but none had required surgery; since publication in July 2002, several have had surgery.

Among the 15 patients in the cohort with osteonecrosis, 93% were homosex-

ual men, 80% were white, 13% were black, and no one used injection drugs. Osteonecrosis was more common in the patients who used systemic corticosteroids, lipid-lowering agents, or testosterone, those who did bodybuilding exercises regularly, and those with detectable levels of anticardiolipin antibodies. It is unclear if the factor of bodybuilding is incidental or causal. Miller and colleagues postulated that bodybuilding could amplify intra-articular forces that initiate injury. It should be stressed that bodybuilding has not been associated with osteonecrosis in other studies and may simply be associated with this cohort only.

These investigators found no association between osteonecrosis and use or duration of use of PIs (most HIV-infected subjects in the study were receiving PIs) and stated that serum lipid levels were only marginally associated with risk of osteonecrosis. However, the significant association of use of lipid-lowering drugs with osteonecrosis suggests that patients with hyperlipidemia may be at increased risk even when lipid levels are currently controlled. Some PIs are associated with increases in lipid levels that often require lipid-lowering therapy. PI treatment thus may be an indirect causal factor in osteonecrosis.

Other studies have reported some association of osteonecrosis with risk factors in addition to PI use or HIV infection itself. Brown and Crane (*Clin Infect Dis*, 2001) found a 0.45% incidence of osteonecrosis, with 3 of the 6 patients with disease having such risk factors as smoking, hyperlipidemia, or steroid use. Scribner and colleagues (*J Acquir Immune Defic Syndr*, 2000) reported traditional risk factors in 22 of 25 patients with osteonecrosis, with increased risk being associated with increasing number of risk factors. All cases occurred in men; 28% had a history of alcohol abuse, 12% had used steroids, and 32% had hyperlipidemia.

Screening of asymptomatic patients for osteonecrosis currently is not recommended. However, any patient with persistent symptoms in the groin or hip should be assessed by MRI. Practitioners should be aware that patients who use short- or long-term steroids or lipid-lowering agents are at increased risk of osteonecrosis. Disease often is progres-

sive. Once symptoms of osteonecrosis develop, weight-bearing activity should be limited, and physical therapy should focus on improving range of motion. Surgical options include core decompression, vascular grafting, and total hip replacement. If osteonecrosis is diagnosed early in the course of the disease, treatment with core decompression is adequate; this is an outpatient procedure with low morbidity. In cases of severe or progressive disease, total hip replacement is usually necessary.

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Case 2: Osteopenia and Osteoporosis

Case Presentation

A 26-year-old HIV-infected man with a CD4+ cell count of 289/ μ L (nadir, 129/ μ L) read an article on the Internet about risk for osteoporosis. On the basis of this information, he wants a prescription for alendronate, a bone resorption inhibitor. He has never taken steroids and currently is a cigarette smoker. He is asymptomatic but believes that taking alendronate will prevent development of osteopenia and osteoporosis.

Discussion

The recently reported National Osteoporosis Risk Assessment Study (Siris et al, *JAMA*, 2001) in more than 200,000 postmenopausal women has provided some surprising findings regarding osteopenia and osteoporosis in the general population. The study showed that 40% of postmenopausal women had osteopenia and 7% had osteoporosis. Risk factors included smoking, glucocorticoid use, and Asian

or Hispanic heritage. Protective factors were greater body mass index, African-American heritage, estrogen use, and diuretic use. Eleven percent of the women had a baseline fracture of the rib, hip, wrist, or spine with minimal trauma by age 45 years. Such findings indicate that osteopenia and osteoporosis are much more common than previously believed, and may raise the suspicion that it is even more common in HIV-infected individuals.

In 1994, the osteoporosis working group of the World Health Organization published a definition for the diagnosis of osteoporosis in epidemiologic studies. They proposed that osteoporosis be defined as having a bone mineral density at the spine, hip, or wrist of 2.5 standard deviations or more below the mean for healthy young adult women, or as having a history of atraumatic fracture (Nelson et al, *Ann Intern Med*, 2002). Hence, osteoporosis is now defined as a bone mineral density test T score of less than -2.5 in women, with risk of fracture doubling with each standard deviation decrease in T score. The relationship between bone mineral density and fracture risk in men is undefined, and a T score of -2.5 in men actually represents a greater bone mineral density than in women. However, men with a maternal history of osteoporosis are at a 1.5-fold greater risk of disease than men without this background. Men develop hip fractures later in life and vertebral fractures earlier than women.

Data on osteopenia and osteoporosis in patients with HIV disease are confusing. A number of studies have been performed to elucidate the etiology of the disorder, with attention to the potential roles of potent antiretroviral therapy and PI treatment. Thus far, however, the role of such treatment remains unclear, and data in this regard are often conflicting. Many investigators have speculated that HIV infection in association with cytokine activation, direct infection of osteogenic cells, or hypogonadism may play a role in osteopenia and osteoporosis. Corticosteroid use, decreased physical activity, malnutrition, malabsorption, and smoking may play a role in disease in both HIV-infected and HIV-uninfected persons.

Lawal and colleagues (*AIDS*, 2001) studied 36 malnourished HIV-infected

men during the era prior to potent antiretroviral therapy, and 19 men and 3 women receiving potent therapy who had fat redistribution. On average, the patients receiving potent therapy were 15 kg heavier. No differences between the 2 groups were observed with regard to bone mineral content, bone calcium, or bone mineral density, but both groups had lower values for all 3 measures than did a group of HIV-uninfected patients.

In another study, Paton and colleagues (*Calcif Tissue Int*, 1997) found no difference in total bone mineral density or hip bone mineral density between 45 HIV-infected men treated in the pre-potent therapy era and a group of age-matched HIV-uninfected controls. HIV-infected patients had a 3% lower lumbar spine bone mineral density than control subjects, and 15 of the HIV-infected patients showed a 1.6% decline in total bone mineral density from baseline over 16 months of follow-up.

Carr and colleagues investigated whether osteopenia and osteoporosis might be associated with hyperlactatemia or mitochondrial disease (AIDS, 2001). They found that among 32 antiretroviral-naïve patients, 42 patients receiving nucleoside reverse transcriptase inhibitor (NRTI) therapy, and 147 receiving PI plus NRTI therapy, independent predictors of disease were higher pretreatment lactate levels (odds ratio, 2.39 per 1 mmol/L increase) and lower pretreatment body weight (marginally significant with an odds ratio of 1.06). They found no association between type or duration of PI treatment and bone changes or between lipodystrophy and bone changes. Overall, lower body weight was associated with lower total bone mineral density, and higher lactate levels were associated with lower bone mineral density of the spine. Claxton and colleagues (8th CROI, 2001), however, performed a similar study and found no association between lactate levels and bone mineral density. In another study, Tebas and colleagues (AIDS, 2000) found no association between visceral adiposity and osteopenia. However, Huang and colleagues (AIDS, 2001) did find an association between visceral adiposity and osteopenia.

More recently, Mondy and colleagues (9th CROI, 2002) reported a

The role of potent antiretroviral therapy in the etiology of osteopenia and osteoporosis remains unclear

study in which 108 men and 17 women with a mean age of 41 years were assessed by dual-energy x-ray absorptiometry at baseline and at 48 and 72 weeks. Forty-six percent of the patients were found to have osteopenia or osteoporosis. Low bone mineral content was associated with a greater degree of weight loss and wasting, prior steroid use, past or current cigarette smoking, and longer duration of potent antiretroviral therapy. PI use was not significantly associated with low bone mineral density. Spine and hip bone mineral density increased by 3% and 2%, respectively, in the patient group over 72 weeks.

An additional suggestion that PI use may not be the primary culprit in osteopenia and osteoporosis came from a randomized study by Hoy and colleagues (2nd Int Conf Adverse Drug React Lipodystrophy HIV, 2000), in which discontinuation of PI treatment produced no change in bone mineral density over 48 weeks. Further, Amiel and colleagues (9th CROI, 2002) found that levels of osteocalcin, which is a marker for bone formation, were decreased in untreated patients and in treated patients not receiving a PI compared with patients receiving PI-containing therapy. Aukrust and colleagues (*J Clin Endocrinol Metab*, 1999) found that PI treatment was associated with increased osteocalcin. Previously, Wang and colleagues (8th CROI, 2001) had found that indinavir blocks in vitro and in vivo differentiation and function of osteoblasts. More recently, Wang and colleagues (9th CROI, 2002) found that administration of indinavir in mice for 5 weeks resulted in a 17% to 20% decrease in bone miner-

al density in lumbar vertebrae, tibia, and femur; a decrease in both cortical and trabecular bone mass; and a 25% decrease in bone volume, with the total number of osteoclasts and osteoblasts remaining unchanged.

These data provide little overall guidance for the HIV care practitioner in reducing risk of osteopenia and osteoporosis. Perhaps the guiding principle in this arena is to change what can be changed and accept what cannot be changed until the arrival of more definitive data. Thus, patients should be encouraged to stop smoking, to engage in weight-bearing exercise, and to practice good bone health by intake of the recommended 1.2 to 1.5 g of calcium and 400 to 800 units of vitamin D per day. A high threshold for withholding even short courses of systemic steroids should be maintained. Hypogonadism should be treated, since testosterone is important in suppressing osteoclast action, and wasting should be treated.

It is important to recognize that patients aged 45 years or older are at increased risk of osteopenia and osteoporosis, as are postmenopausal women. The most recent National Institutes of Health consensus statement on this subject indicates that bone mineral density screening should be performed in all patients receiving steroid treatment for 2 months or longer irrespective of age, as well as in all postmenopausal women. Screening is also recommended in other patients with conditions that put them at risk. Specific recommendations for screening in men currently are being formulated. In practice, screening in HIV-infected patients should be individualized, based on assessment of risk factors and the recognition that risk of osteopenia and osteoporosis increases with age and multiple risk factors. It is expected that clearer recommendations regarding screening for HIV-infected patients will be forthcoming in the relatively near future.

In the case described above, the patient did not receive alendronate after his initial presentation. The patient and his provider discussed his family history (he had no maternal or paternal risk factors), and his personal history revealed no risk factors other than smoking. (If it was determined that he had a number of risk factors, a dual-energy x-ray absorp-

tiometry scan would have been ordered.) The patient and his provider focused on increasing his intake of calcium and vitamin D and beginning an exercise program. The patient is now contemplating a smoking-cessation program.

Case 3: Hypertension

Case Presentation

A 36-year-old woman without prior knowledge of her HIV infection status presented for the first time in May 1996 with a CD4+ cell count of 11/ μ L, *Pneumocystis carinii* pneumonia, alopecia, and herpes simplex virus infection. Her plasma HIV-1 RNA level was greater than 500,000 copies/mL. She was started on indinavir/stavudine/lamivudine. After 1 month, her viral load was below the assay detection limit and her CD4+ cell count was 25/ μ L; her condition continued to improve thereafter. In December 1997, she developed hypertension. The patient had gained 14 kg while on antiretroviral therapy; she had no family history of hypertension or evidence of any secondary causes of hypertension, and she was not using alcohol, injection drugs, or tobacco.

Discussion

Since body weight is a modifiable risk factor for hypertension, the patient should be encouraged to lose weight. Many practitioners would also substitute another PI for indinavir in this setting, on the basis of evidence demonstrating an association of indinavir treatment with hypertension. For example, a study by Cattelan and colleagues (AIDS, 2001) showed that 31 of 118 patients with no renal abnormalities who were receiving indinavir developed hypertension of stage 1 or greater (6 with stage 3, 5 with stage 2, 20 with stage 1), compared with none of 77 patients receiving other PIs (nelfinavir, saquinavir, or ritonavir) over a median 34 months of follow-up. The mean blood pressure in the indinavir group was 125/81 mm Hg at baseline and 136/91 mm Hg at the end of follow-up. The 31 patients who developed hypertension had a mean blood pressure of 153/100 mm Hg at the end of follow-up. In the

group not receiving indinavir, mean blood pressure was 126/82 mm Hg at baseline and 125/80 mm Hg at the end of follow-up. Among the patients who developed hypertension, 18 (58%) had a family history of hypertension. The hypertension was controlled with medication in 18 patients. Of 9 patients who stopped indinavir therapy, hypertension resolved in 4 and persisted in 5.

These data suggest that indinavir treatment is associated with hypertension, although the mechanism of this effect remains unclear. Patients on indinavir should be evaluated for hypertension at every visit, and discontinuation of the drug should be considered if hypertension develops. It may be appropriate to consider indinavir as a second-line PI in patients with hypertension or a family history of hypertension. With regard to potential mechanisms of the hypertensive effect, it may be that indi-

navir acts as a catalyst for latent hypertension in individuals with a genetic predisposition for the disorder. Additional studies are needed to assess the roles of obesity, alcohol use, non-steroidal anti-inflammatory drugs, tobacco, concomitant trimethoprim/sulfamethoxazole use, and prior use of antivirals in promoting hypertension in HIV-infected patients.

Untreated hypertension is responsible for serious end organ complications of the renal and cardiovascular system and thus needs to be screened for and treated in HIV-infected patients. Among the available antihypertensive agents, angiotensin-converting enzyme inhibitors are suited for those patients with renal disease or diabetes; however, African Americans with a low renin state may not respond to such treatment. Calcium channel blockers are suited for use in patients with a low renin state,

Table 1. Drug-Drug Interactions Between Antiretroviral Agents and Antihypertensive or Antiarrhythmic Agents

Nucleoside Reverse Transcriptase Inhibitors
<ul style="list-style-type: none"> • Avoid using thiazide or loop diuretics with didanosine because of increased risk of pancreatitis. When the drugs are used together, the risk of pancreatitis is increased. If didanosine or a thiazide is used alone, each is associated with risk of pancreatitis. Used together, the risk is even greater.
Nonnucleoside Reverse Transcriptase Inhibitors
<p><i>Cytochrome P450 interactions are key.</i></p> <ul style="list-style-type: none"> • Efavirenz: Monitor clinical effects of all calcium channel blockers, including dihydropyridines (eg, nifedipine, nifedipine, nitrendipine). • Nevirapine: Theoretical risk for calcium channel blockers to vary in efficacy over time.
Protease Inhibitors
<p><i>Cytochrome P450 interactions are key.</i></p> <ul style="list-style-type: none"> • Amprenavir: Do not use with bepridil. May increase concentration of calcium channel blockers. • Indinavir: Significant interactions with calcium channel blockers and quinidine. • Lopinavir/ritonavir: Close monitoring is suggested with use of calcium channel blockers. • Nelfinavir: May result in high calcium channel-blocker levels. Amiodarone and quinidine should not be used with nelfinavir. • Ritonavir: Absolute contraindications include concurrent use with amiodarone, encainide, flecainide, propafenone, quinidine, and bepridil. Increases in area under the concentration-time curve (AUC) with multiple medications, including lidocaine, mexiletine, warfarin; metoprolol, pindolol, timolol; and all calcium channel blockers. Moderate decrease or increase in AUC with S-warfarin and losartan. Possible increase in AUC with doxazosin, prazosin, terazosin, digoxin, and tocainide.

diabetes, or renal disease. Beta blockers are suited for use in younger patients with good cardiac conduction function. Their use requires attention to the potential for increased glucose, insulin, and triglyceride levels and decreased high-density lipoprotein cholesterol level. Caution should be exercised in using calcium channel blockers and beta blockers together because of the risk of cardiac conduction abnormalities. Both calcium channel blockers and beta blockers may be associated with sexual dysfunction. Diuretics can be used in first-line treatment or to augment other antihypertensive drugs. With diuretic use, patients should be monitored for electrolyte levels, hyperuricemia, and mild increases in cholesterol, glucose, and insulin levels.

There are a number of important interactions between antiretroviral agents and antihypertensive drugs that must be considered in deciding on antihypertensive treatment options. Most of these consist of nonnucleoside reverse transcriptase inhibitor (NNRTI) and PI interactions with antihypertensive agents mediated via the cytochrome P450 system (see Table 1). PIs, particularly ritonavir, also exhibit a number of important interactions with antiarrhythmic agents.

The patient discussed in this case stopped taking indinavir, but her hypertension did not resolve. Fortunately, it has been well controlled with labetalol. Three years after the events of this case, the patient became pregnant and delivered a healthy baby boy in 2002.

Case 4: Mitochondrial Toxicity

Case Presentation

A 52-year-old man was first diagnosed with HIV infection in April 1998. His plasma HIV-1 RNA level was 36,000 copies/mL and CD4+ cell count was 253/ μ L. The patient wished to begin antiretroviral therapy and was started on a regimen of indinavir/stavudine/lamivudine. At 16 weeks, the patient's plasma HIV-1 RNA level was less than 50 copies/mL and CD4+ cell count was 448/ μ L. At week 60, the patient complained of mild burning pain in the lower extremities and increased abdom-

inal girth. He also had intermittent nausea and fatigue, and experienced shortness of breath on exertion, but denied having chest pains. Laboratory results at this time showed plasma HIV-1 RNA level of less than 50 copies/mL; CD4+ cell count of 420/ μ L; normal white blood cell count and differential; packed cell volume, 41%; sodium, 142 mEq/L; potassium, 4.1 mEq/L; chloride, 100 mmol/L; bicarbonate, 20 mEq/L; normal serum creatinine; blood urea nitrogen, 21 mg/dL; glucose, 172 mg/dL; aspartate aminotransferase, 36 U/L; alanine aminotransferase, 30 U/L; alkaline phosphatase, 134 mU/mL; triglycerides, 487 mg/dL; cholesterol, 218 mg/dL; and total bilirubin, 2.2 mg/dL (1.7 indirect). Possible management choices for this patient include continuing the current antiretroviral regimen, with reevaluation in 2 weeks; changing the regimen; and stopping all antiretroviral therapy.

Discussion

This patient's symptoms and laboratory results are consistent with lactic acidosis due to mitochondrial toxicity. Antiretroviral therapy should be stopped, since this is a life-threatening condition, with mortality ranging from 30% to 60%. The goal in managing mitochondrial toxicity is to diagnose it as early as possible. Early symptoms include fatigue, abdominal pain, weight loss, malaise, nausea, vomiting, and anorexia, with axonal neuropathy sometimes present. These symptoms worsen as toxicity progresses. The evolution of the disorder may be fulminant or insidious, and symptoms can develop after years of tolerating nRTI treatment. In any patient presenting with such symptoms, the bicarbonate level should be checked and anion gap calculated; the venous lactate level should be measured if the condition is suspected. The threshold of suspicion for this disorder should be very high in any patient presenting with these symptoms. It is noteworthy that women, particularly those with greater body mass index, have accounted for a disproportionate number of the cases of lactic acidosis reported thus far.

Treatment with stavudine appears to be associated with mitochondrial toxicity, and the use of stavudine and didano-

sine together appears to augment the risk (Boubaker et al, *Clin Infect Dis*, 2001; Coghlan et al, *Clin Infect Dis*, 2001). Zidovudine has also been associated with such toxicity. Potent therapy including nRTIs other than zidovudine and stavudine can usually be safely instituted once toxicity has resolved. Routine monitoring of lactate levels is not recommended in patients receiving potent therapy including nRTIs. There is considerable evidence that mild elevations of serum lactate levels are common in asymptomatic patients receiving nRTIs (estimated incidence, 15%-35%), with such elevations being chronic and compensated (John et al, *AIDS*, 2001). The mild hyperlactatemia in such patients has a poor predictive value for development of symptomatic lactic acidosis.

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Suggested Reading

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