

## *Osteonecrosis in Patients With Acquired Immunodeficiency Syndrome (AIDS): Report of Two Cases and Review of the Literature*

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### RESUMO

**Osteonecrose em Pacientes Com Síndrome de Imunodeficiência Humana Adquirida (SIDA): Relato de Dois Casos e Revisão da Literatura.**

Um aumento na incidência de anormalidades no metabolismo ósseo-mineral (osteopenia/osteoporose) tem sido observado em pacientes com síndrome de imunodeficiência humana adquirida (SIDA). Relatamos dois casos de osteonecrose em pacientes com SIDA. Ambos os pacientes estavam recebendo terapia anti-retroviral de alta potência (HAART) e apresentavam um ou mais fatores de risco conhecidos para osteonecrose. Nós revisamos a literatura e discutimos a patogênese, diagnóstico, prevenção e tratamento desta patologia em pacientes com SIDA. (**Arq Bras Endocrinol Metab 2005;49/6:996-999**)

**Descritores:** Osteonecrose; SIDA; Terapia anti-retroviral

### ABSTRACT

An increase in the incidence of abnormalities on bone and mineral metabolism (osteopenia/osteoporosis) and the development of osteonecrosis has been observed in patients with acquired immunodeficiency syndrome (AIDS). Two cases of osteonecrosis in patients with AIDS are reported. Both patients were receiving highly active antiretroviral therapy (HAART) and presented with one or more known risk factors for osteonecrosis. We review the literature and discuss the pathogenesis, diagnosis, prevention and treatment of this entity in patients with AIDS. (**Arq Bras Endocrinol Metab 2005;49/6:996-999**)

**Keywords:** Osteonecrosis; AIDS; HAART

**T**HE AVAILABILITY OF HIGHLY active antiretroviral therapy (HAART) since the past decade has resulted in a dramatic reduction in HIV (Human Immunodeficiency Virus) -associated morbidity and mortality in the developed world (1). However, as life expectation increased, new complications emerged, such as insulin resistance, glucose intolerance, dyslipidemia, lipodystrophy, lactic acidemia and osteopenia (2). An increase in the incidence of abnormalities of bone and mineral metabolism (osteopenia/osteoporosis) and the development of avascular necrosis, also known as osteonecrosis, has been observed. The etiology and pathogenesis of osteonecrosis in these patients is unknown, but there are several hypotheses. We report two cases of osteonecrosis in patients with AIDS and discuss the pathogenesis, diagnosis, prevention and treatment.

## CASE REPORTS

Patient 1, a 45-year-old woman, HIV-positive diagnosed in 1993, started antiretroviral therapy in 1995 with zidovudine (monotherapy) and used megestrol acetate 800mg/day for wasting syndrome. In 2002, she presented with acute pain in the left hip triggered by weight bearing. The bone mineral density was compatible with hip and lumbar spine osteopenia. Pelvic X-ray showed irregularity of the left femoral head (figure 1). Magnetic Resonance Imaging showed a linear area of abnormal signal in the left femoral head, suggesting severe subchondral ischemia, and bone edema in the left femoral head and neck (figure 2). Total joint arthroplasty was proposed, but the patient refused this treatment. Clinical, densitometric and biochemical data are shown in table 1.

Patient 2, a 41-year-old woman, HIV-positive diagnosed in 1995, when zidovudine was started as monotherapy. In 1996, she was hospitalized because of a demyelinating neuropathy that was treated with systemic corticosteroids for eight months. In 1997, she presented with acute pain in the left hip. Mild avascular necrosis was diagnosed, and she was assigned for physical therapy. Osteoporosis of lumbar spine and hip was detected by bone densitometry and calcitonin was started. In 1998, disfiguring alterations in body shape resulted in two plastic surgeries (abdominal and buffalo hump), with temporary improvement. Clinical, densitometric and biochemical data are shown in table 1.

## DISCUSSION

There have been many case reports of osteonecrosis occurring in patients with AIDS in the last decade. It



**Figure 1.** Pelvic X-ray: Irregularity of the left femoral head (arrowheads).

has been suggested that osteonecrosis in this population may be caused by an increased prevalence of risk factors, including the use of corticosteroids and megestrol acetate, hypertriglyceridemia, ethanol abuse, local trauma and hypercoagulable states (3,4). The relation between osteonecrosis and the use of protease inhibitors (PI) has been challenged because cases of osteonecrosis were reported before the availability of this group of antiretroviral drugs and even in patients without any treatment (5).

One or more risk factors can be identified in approximately 80% of all cases of osteonecrosis in the HIV- population. The remaining 20% are considered to be idiopathic. Some of these risk factors occur frequently in HIV+ patients (table 2).

The pathogenesis of osteonecrosis induced by alcoholic beverages, corticosteroids and megestrol acetate is not well established. However, all of them have deleterious effects in lipid metabolism.

Dyslipidemia is common in patients HIV+, mainly associated with the use of HAART. Both hypertriglyceridemia and hypercholesterolemia can induce fatty infiltration of the bone marrow, which could obstruct local blood flow (6).

Corticosteroids are used in the management of various conditions related or not to the HIV-infection. Our patient 2 received corticosteroids for eight months due to a neurological condition. Several studies suggest that the use of corticosteroids is the most common factor related to osteonecrosis in HIV-positive patients (7).

Megestrol acetate, a synthetic progestational steroid used in patients with wasting syndrome (8), can act like a glucocorticoid, binding to DNA glucocorticoid response elements and predisposing patients to osteonecrosis. Patient 1 received this drug for a long time.



**Figure 2.** Magnetic Resonance (T1Weighted): hypointense signal of the left femoral head (arrowheads).

**Table 1.** Patients' characteristics at the time of osteonecrosis.

Characteristics	Patient 1	Patient 2
Viral load (copies/mL)	421	undetectable
Antiretroviral Therapy	Zidovudine/Lamivudine/ Indinavir/Ritonavir	Zidovudine/Lamivudine/ Saquinavir
Glucose (mg/dL)	84	80
Cholesterol (mg/dL)	225	248
Triglyceride (mg/dL)	410	283
T-score lumbar spine	-1,6	-2,6
T-score femoral neck	-1,4	-2,5
Anti-cardiolipin	Non-tested	Negative

**Table 2.** Risk factors for osteonecrosis.

Alcohol abuse	Chemotherapy
Dyslipidemia	Radiotherapy
Gaucher's Disease	Rheumatoid arthritis
Hemoglobinopathies	Systemic corticosteroids
Hypercoagulable states	Systemic Lupus Erythematosus
Megestrol acetate	Trauma
Osteomyelitis	Vasculitis
Osteopenia/Osteoporosis	Idiopathic
Pregnancy	

Several vasculitideses have been associated to HIV infection, but the pathogenesis is unknown (9). It is estimated that anticardiolipin antibodies are present in 50–86% of all HIV-infected patients, which may have a role in the development of osteonecrosis in patients with AIDS. The mechanisms involved could be endothelium injury or vascular thrombosis, leading to bone necrosis (10). Our patient 2 did not have anticardiolipin antibodies, and patient 1 was not tested. The acquired deficiency of protein S, a natural antithrombotic factor, may play a role in the osteonecrosis of these patients since HIV-infection is associated with this condition and with the presence of anti-protein S antibodies (11).

The association of HAART and osteonecrosis is controversial. Some studies have reported a greater frequency of osteonecrosis in patients using HAART than in the general population, raising the hypothesis that HAART could act as a risk factor for osteonecrosis (12-14). In contrast, two case series (4,15) and two case-control studies (6,16) have concluded that the use of HAART is not independently associated with osteonecrosis. This association may have some bias. First, the probability that an HIV-positive patient with osteonecrosis is taking HAART nowadays is high. Second, the use of HAART promoted an increase in life expectancy, which may give patients the opportunity of developing osteonecrosis due to other factors. Nevertheless, HAART may contribute to the development of osteonecrosis by secondary effects on lipids (2,17).

Clinical presentation of osteonecrosis is generally insidious, although it can be acute, as in the cases here reported. The majority of patients complain of mild to moderate pain in the periarticular region. The pain is triggered by weight bearing or by moving the affected limb toward the extreme outer ranges of mobility. Physical examination is inconsistent, but can reveal limitation of mobility and periarticular tenderness (18).

In spite of unspecific abnormalities found on history and physical examination, any patient with HIV-infection that presents with periarticular pain and has one or more of the known risk factors should be investigated for osteonecrosis with imaging studies. Plain x-ray films of the affected articular region have low sensibility, detecting only moderate or advanced osteonecrosis. The classical changes seen in x-ray are: cystic sclerosis, bony collapse and secondary degenerative joint disease. Computed tomography scan can detail some of the specific changes of osteonecrosis, necessary for the staging of osteonecrotic disease (table 3) (19). Magnetic resonance has the best sensibility (> 90%), being useful for the diagnosis of the less severe cases.

There are no clinical guidelines for the treatment of osteonecrosis, only expert recommendations (20). Mild cases can have a conservative management, including physical therapy, the use of analgesics, decreased weight bearing on the affected joint and

**Table 3.** Staging system for osteonecrosis by the association of research circulation osseous (ARCO).

STAGE	CRITERIA
0	All diagnostic studies normal, diagnosis by histology only.
1	Plain radiographs and computed tomography normal, magnetic resonance imaging positive and biopsy positive, extent of involvement A, B, or C (less than 15 percent, 15 to 30 percent, and greater than 30 percent, respectively).
2	Radiographs positive but no collapse, extent of involvement A, B, or C.
3	Early flattening of dome, crescent sign, computed tomography or tomograms may be needed, extent of involvement A, B, or C, further characterization by amount of depression (in millimeters).
4	Flattening of femoral head with joint space narrowing, possible other signs of early osteoarthritis.

minimization of risk factors. Moderate to severe cases must have an aggressive intervention to prevent progression of the lesion, which is achieved with surgery, mainly total joint arthroplasty, but also endoprosthesis and arthrodesis (20).

Prevention of osteonecrosis is achieved by judicious use of corticosteroids and megestrol acetate, treatment of dyslipidemia, anticoagulant therapy in hypercoagulable states and avoiding ethanol abuse (17).

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