Original Article

Osteonecrosis in Patients with Human Immunodeficiency Virus Type 1 Infection in Taiwan

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SUMMARY: Osteonecrosis, a disabling complication associated with antiretroviral therapy (ART) and human immunodeficiency virus (HIV) infection, has rarely been reported in an Asian population. After an observation of 3,250 person-years (PY), 11 of 967 (1.1%) HIV-infected patients at a median age of 34 years developed osteonecrosis involving the hip joints (incidence, 3.4 per 1,000 PY). Their median CD4+ lymphocyte count had increased from 35 cells/μL at the diagnosis of HIV infection to 297 cells/μL at the diagnosis of osteonecrosis. The crude rate of osteonecrosis increased from 0% in patients without exposure to ART to 2.6 and 1.7% in patients with exposure to nucleoside reverse transcriptase inhibitors (NRTIs) and who had undergone highly active antiretroviral therapy (HAART) for 5 years or longer, respectively (P = 0.18 and 0.09, respectively). Among the patients receiving HAART, the estimated incidence of osteonecrosis was 4.2 per 1,000 PY. Patients with osteonecrosis had a longer duration of exposure to NRTIs (1,641 versus 1,264 days, P = 0.26) and to HAART (1,603 versus 1,251 days, P = 0.42), a higher serum triglyceride (median, 1,130 versus 351 mg/dl; P = 0.09), and a higher proportion of lipodystrophy (81.8 versus 15.0%, P < 0.0001). Our report suggests that osteonecrosis is a rare complication in HIV-infected patients with prolonged exposure to ART with resultant metabolic complications.

INTRODUCTION

Osteonecrosis, also known as avascular necrosis, has been increasingly reported in association with human immunodeficiency virus (HIV) infection (1-3) since the first case report in 1990 (4). In a cross-sectional study, 4.4% of HIV-infected patients had asymptomatic osteonecrosis (5). Its morbidity threatens the quality of life and increases the cost of medical care when highly active antiretroviral therapy (HAART) remarkably prolongs life span of patients with HIV infection. Although osteonecrosis has been a well-known illness in the general population, its prevalence is indeed higher in HIV-infected patients (6).

The pathogenesis of osteonecrosis in HIV-infected patients remains unclear (7), although various hypotheses and predisposing factors such as use of corticosteroids, alcoholism, hyperlipidemia, hypercoagulability, and osteoporosis have been proposed with varying strength of evidence by analysis of case series and control studies (1,5,6,8-10). Almost all of those cases were described among HIV-infected patients in Western countries with earlier and better access to antiretroviral therapy (ART); however, the incidence of and factors associated with osteonecrosis are rarely reported in Asian populations. With the increasing expansion of HAART programs in most Asian countries, osteonecrosis is expected to be an emerging threat to long-term successful management of HIV infection when mortality and morbidity related to HIV infection decrease dramatically. In the present study, we aimed to review cases of osteonecrosis in patients receiving HIV care at a university hospital in Taiwan where free access to HAART was begun in 1997.

MATERIALS AND METHODS

Study population: Between June 1994 and December 2003, non-hemophiliac HIV-infected patients aged 15 years or greater were consecutively enrolled in an open cohort study to investigate complications related to HIV infection and ART at the National Taiwan University Hospital (NTUH), a major referral hospital for provision of HIV care in Taiwan (11). The medical records of all patients with HIV infection were periodically reviewed to identify patients who were diagnosed as having osteonecrosis. A standardized case record form was used to retrieve data regarding demographics, risk of HIV transmission, baseline and latest CD4+ lymphocyte count and plasma HIV RNA load (PVL), concomitant medical illness, types and duration of ART and HAART, and serum cholesterol and triglyceride levels. Patients with a diagnosis of osteonecrosis within 1 month of enrollment were excluded from analysis.

ART and HAART were introduced into Taiwan in 1988 and 1997, respectively, and all patients with HIV infection were offered free access to HIV care and HAART in designated hospitals around Taiwan. HAART was prescribed as clinically indicated by the following and updated US Department of Health and Human Services guidelines (12).

Laboratory and radiographic investigations: Blood biochemistry tests, including cholesterol and triglyceride, CD4+ count and PVL, were determined every 3 to 4 months. PVL...
was quantified using the Cobas Amplicor HIV-1 Monitor test (Cobas Amplipcr version 1.5; Roche Diagnostics Corp., Indianapolis, Ind., USA) with a lower detection limit of 400 (2.60 log10) copies/mL, and CD4+ count was determined using FACFlow (BD FACS Calibur; Beeton Dickinson, San Jose, Calif., USA).

Patients with joint pain were subjected to radiographic examinations after evaluation by the treating physicians, including plain radiography and magnetic resonance imaging (MRI). Bone mineral density (BMD) as determined by dual energy X-ray absorptiometry (DEXA, Hologic QDR-4500A; Hologic, Waltham, Mass., USA) was performed on an as-needed basis. Osteonecrosis was diagnosed by the characteristic radiographic findings on plain joint radiography or MRI interpreted by radiologists blinded to the status of HIV-infected patients, and all of the radiographic examinations were reviewed by one of the co-authors (TTF Shih).

**Definitions:** HAART was defined as the combination of at least three antiretroviral agents containing nucleoside reverse transcriptase inhibitors (NRTIs) plus protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), or triple NRTIs. Lipodystrophy was defined by clinical presentations of peripheral fat wasting (face, arms, buttocks, or legs) or central fat accumulation (abdomen or dorsocervical pad) observed by the treating physicians (13). Weight change without peripheral fat wasting or central adiposity was not classified as lipodystrophy.

**Statistical analysis:** All statistical analyses were performed using SPSS software (version 12.0; SPSS, Inc., Chicago, Ill., USA). Categorical variables were compared using χ2 or Fisher’s exact test whereas non-categorical variables were compared using Wilcoxon’s rank-sum test. Point estimation was calculated using SPSS software (version 12.0; SPSS, Inc., Chicago, Ill., USA). Osteonecrosis was diagnosed by the characteristic radiographic findings on plain joint radiography or MRI interpreted by radiologists blinded to the status of HIV-infected patients, and all of the radiographic examinations were reviewed by one of the co-authors (TTF Shih).

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**Statistical analysis:** All statistical analyses were performed using SPSS software (version 12.0; SPSS, Inc., Chicago, Ill., USA). Categorical variables were compared using χ2 or Fisher’s exact test whereas non-categorical variables were compared using Wilcoxon’s rank-sum test. Point estimation for Poisson distribution was used for estimating the incidence and 95% confidence intervals (CI) of osteonecrosis. Univariate analysis was used to identify the factors associated with osteonecrosis, such as age, sex, risk behavior for HIV transmission, baseline CD4 count and PVL, initial presentation of AIDS-related diseases, and use and duration of ART and HAART. All tests were two-tailed and a P value <0.05 was considered significant. The observation duration of affected patients was estimated from date of enrollment to diagnosis of osteonecrosis, while that of patients without osteonecrosis was estimated from date of enrollment to death, the last follow-up at this hospital and other designated hospitals in Taiwan, or the end of this observational study on 31 December, 2005.

**RESULTS**

Over a 9-year study period, 968 patients sought HIV care at the NTUH and 12 patients received a diagnosis of osteonecrosis. One patient who presented to this hospital because of an established diagnosis of HIV infection and osteonecrosis at another hospital was excluded, and therefore 11 patients were enrolled in this study. Demographics, clinical, immunological, and virological characteristics of the 11 patients with osteonecrosis and 956 patients without osteonecrosis are shown in Table 1. Patients with and those without osteonecrosis did not differ in demographics and baseline clinical, immunologic, and virological characteristics. All of the patients with osteonecrosis were males and had depleted CD4+ counts (median, 35 cells/μL), while 72.7% had AIDS-defining opportunistic illnesses when HIV infection was diagnosed.

Osteonecrosis developed in patients with prolonged exposure to ART and HAART. The median interval between

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with osteonecrosis</th>
<th>Patients without osteonecrosis</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient, no.</td>
<td>11</td>
<td>956</td>
<td>967</td>
<td></td>
</tr>
<tr>
<td>Age, median (range) (y)</td>
<td>34 (30, 47)</td>
<td>34 (15, 83)</td>
<td>34 (15, 83)</td>
<td>0.64</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>11 (100)</td>
<td>884 (92.5)</td>
<td>895 (92.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Risk factor, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual/bisexual</td>
<td>4 (36.4)</td>
<td>583 (61.0)</td>
<td>587 (60.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>6 (54.6)</td>
<td>310 (32.4)</td>
<td>316 (32.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Others</td>
<td>1 (9.1)</td>
<td>63 (6.6)</td>
<td>64 (6.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>AIDS at baseline, no. (%)</td>
<td>9 (81.8)</td>
<td>650 (68.9)</td>
<td>659 (69.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>AIDS-OI at baseline, no. (%)</td>
<td>8 (72.7)</td>
<td>535 (56.0)</td>
<td>543 (56.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>CD4+ lymphocyte count at baseline, median (range), cells/μL</td>
<td>35 (3, 710)</td>
<td>76.5 (0, 1,202)</td>
<td>73 (0, 1,202)</td>
<td>0.21</td>
</tr>
<tr>
<td>PVL at baseline, median (range) (log10), copies/mL</td>
<td>4.58 (2.60, 5.78)</td>
<td>5.19 (2.60, 5.88)</td>
<td>5.19 (2.60, 5.88)</td>
<td>0.30</td>
</tr>
<tr>
<td>Lipodystrophy, no. (%)</td>
<td>9 (81.8)</td>
<td>143 (15.0)</td>
<td>152 (15.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipemia &gt; 2 times, no. (%)</td>
<td>4 (50.0)</td>
<td>174 (32.2)</td>
<td>178 (32.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>Peak triglyceride, (range) mg/dl</td>
<td>1,130 (301, 2,190)</td>
<td>351 (201, 3,200)</td>
<td>351 (201, 3,200)</td>
<td>0.09</td>
</tr>
<tr>
<td>Peak cholesterol, (range) mg/dl</td>
<td>287 (225, 401)</td>
<td>256.5 (40, 618)</td>
<td>257 (40, 618)</td>
<td>0.40</td>
</tr>
<tr>
<td>Duration of exposure to NRTI, (range) days</td>
<td>1,641 (452, 4,631)</td>
<td>1,264 (0, 5,854)</td>
<td>1,281 (0, 5,854)</td>
<td>0.26</td>
</tr>
<tr>
<td>Duration of exposure to HAART, (range) days</td>
<td>1,603 (452, 2,254)</td>
<td>1,251 (0, 3,533)</td>
<td>1,261 (0, 3,533)</td>
<td>0.42</td>
</tr>
<tr>
<td>Duration of exposure to PIs, (range) days</td>
<td>1,056.5 (156, 1,977)</td>
<td>820 (0, 3,447)</td>
<td>825.5 (0, 3,447)</td>
<td>0.55</td>
</tr>
<tr>
<td>Total observation duration (person-years)</td>
<td>46</td>
<td>3,204</td>
<td>3,250</td>
<td>0.12</td>
</tr>
</tbody>
</table>

AIDS-OI, AIDS defining opportunistic illness; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PIs, protease inhibitors; PVL, plasma HIV RNA load.
initiation of NRTIs, PIs, and HAART and development of osteonecrosis was 1,641 days (range, 452 to 4,631 days), 1,056.5 days (range, 156 to 1,977 days), and 1,603 (range, 452 to 2,254 days), respectively. After HAART, patients with osteonecrosis had a good immunologic response with a median CD4+ count increase of 275 cells/μl (range, -15 to 925 cells/μl), from 35 cells/μl at baseline to 297 cells/μl (range, 25 to 927) (P < 0.0001), with 54.6% of the patients achieving undetectable PVL at the diagnosis of osteonecrosis. Compared with patients without osteonecrosis, patients with osteonecrosis had higher peak triglyceride levels (1,130 versus 351 mg/dl, P = 0.09) and a higher proportion of lipodystrophy (81.8 versus 15.0%, P < 0.0001) when osteonecrosis was diagnosed.

The total observation duration of the cohort was 3,250 person-years (PY); therefore, the overall incidence rate of osteonecrosis of the cohort was 3.4 per 1,000 PY (95% CI, 3.2, 3.6 per 1,000 PY). The incidence rate of osteonecrosis in patients exposed to NRTIs and HAART was 4.2 per 1,000 PY (95% CI, 3.9, 4.4 per 1,000 PY) and 4.2 per 1,000 PY (95% CI, 4.0, 4.5 per 1,000 PY), respectively. Longer duration of exposure to NRTIs and HAART was associated with increased risk of osteonecrosis, which increased from 0% in those without ever exposure to NRTIs and HAART to 2.6 and 1.7% in those with exposure to NRTIs and HAART for 5 years or greater, respectively (P = 0.18 and P = 0.09, respectively).

Of the 11 patients diagnosed with osteonecrosis, 10 had involvement of 20 hip joints with severity grading of 3 to 4, and one had involvement of bilateral knee joints with a severity grading of 3. All of the patients underwent assessment of BMD and their median BMD was 0.9165 g/cm² (range, 0.6090 to 1.107 g/cm²) and median T-score was −0.81 (range, −2.93 to 0.69); 3 were diagnosed with osteoporosis and 3 osteopenia. Bilateral hip joint replacement was performed in 4 patients and unilateral hip joint replacement in 1 patient because of progression of pain and limitation of ambulation. Eight patients received alendronate when it was found to be of benefit in delaying progression of osteonecrosis (14); however, 3 patients finally underwent bilateral hip joint replacement because of progression of symptoms, while three others experienced persistent symptoms but declined the suggestion of surgical intervention and 2 patients continued to receive alendronate with stable disease status clinically and radiographically by MRI (Fig. 1A-D).

**DISCUSSION**

HIV-infected patients were reported to have a 100-fold greater risk of developing osteonecrosis than the general population (15), although the incidence of osteonecrosis is likely underestimated because only patients with disabling joint symptoms underwent MRI. In a cross-sectional survey of 339 asymptomatic patients, up to 4.4% of osteonecrosis was documented by MRI (5). The incidence of MRI-diagnosed osteonecrosis (0.65 cases per 100 PY) was found to be greater than the incidence of osteonecrosis that is symptomatic (0.26 cases per 100 PY) (15). The annual incidence of symptomatic osteonecrosis in HIV-infected patients was reported to be 0.080 - 1.33% (2, 7, 9). The differences of incidence rates among the published studies may vary with study population, co-morbidity, and duration of HIV infection and exposure to ART. For example, the estimated incidence rate of osteonecrosis in our population (4.0 per 1,000 PY) is higher than that of a French study (0.45 per 1,000 PY) (1), which may be related to the fact that our enrolled patients had a lower CD4+ count (73 versus 280 cells/μL), a lower proportion of them were intravenous drug abusers (6.6 versus 19.4%); a higher proportion had AIDS (69 versus 20.5%), and our patients had a longer duration of exposure to ART.
Although no definite etiology of osteonecrosis is identified, various risk factors have been proposed, including alcohol consumption (10), steroids exposure (5,10), dyslipidemia (16), use of lipid-lowering agents (5), testosterone exposure (5), body-building (5), antiphospholipid antibody (5), HIV infection (1), and HAART (1,17). HIV infection itself, through increased antiphospholipid antibody production (16), may promote intraosseous platelet aggregation resulting in bone necrosis (17,18). The immunological response to treatment, which may be evaluated by an increase in CD4+ cell counts from nadir, was found to be associated with osteonecrosis (8).

Whether ART is a direct cause of osteonecrosis has been debated. The adjusted relative risk was reported to increase from 2.6 among patients who had been treated with ART for less than 12 months to 9.6 among those treated for more than 60 months (1). In our study, longer duration of exposure to NRTIs and HAART appeared to be associated with increased risk of osteonecrosis, which increased from 0% in those with no exposure to NRTI and HAART to 2.6 and 1.7% in those with exposure to NRTIs and HAART for 5 years or greater, respectively ($P = 0.18$ and $P = 0.09$, respectively). PIs have been suggested as a link to osteonecrosis (17,19,20), although some studies disagree with this suggestion (1,3,5,7,9,10,21).

Although each antiretroviral agent has been examined for the combination therapy is the standard of care and a change in correlation with osteonecrosis (10), it is difficult to attribute the effect to any single class of antiretroviral agents because combination therapy is the standard of care and a change in therapies is common.

HAART-related dyslipidemia may accelerate the atherosclerotic process and occlude the bone-feeding vessels, which may contribute to avascular necrosis (16,18,22). However, dyslipidemia may be either a cause of osteonecrosis, or simply, a reflection of prolonged treatment and duration of HIV infection. In our study, patients with osteonecrosis had a significantly higher incidence of lipodystrophy (84.6 versus 14.8%, $P < 0.0001$). Lawson-Ayai et al. also described an increased risk of osteonecrosis in patients with lipodystrophy (adjusted matched OR, 64.06, $P = 0.09$) (10). Lipodystrophy has been estimated to be 20–84% in HIV-infected patients (23-25), while 20–50% of patients were estimated to develop lipodystrophy within 2 years of HAART exposure (24,25).

Therefore, increased risk of osteonecrosis in patients exposed to a longer duration of HAART implies not only the immunologic and metabolic effects of HAART on osteonecrosis, but also the duration of HIV infection. Although no effective treatment has been developed to date (26), lipodystrophy may potentially be a marker for clinicians to increase their vigilance of osteonecrosis.

The causal relationship of lipodystrophy and osteonecrosis remains unclear. In HIV-infected patients with lipodystrophy, Jan et al. (27) reported lower leptin mRNA levels, higher interleukin (IL)-6 levels, and higher tumor necrosis factor (TNF)-α mRNA levels. Leptin, an adipokine, was reported to be associated with diminished bone mineral density (28,29). Peripheral leptin administration in obese leptin-resistant mice was reported to have a stimulating effect on bone growth (29,30). Sighinolfi et al. (19) suggested that HIV itself, through increased production of IL-6 and TNF-α, could be associated with osteonecrosis, which imply that HIV infection, with a resultant increase in the production of proinflammatory cytokines, may be associated with both lipodystrophy and osteonecrosis.

Adiponectin, another adipocytokine, was reported to be lower in serum and adipose tissue in lipodystrophic, HIV-infected patients receiving HAART than in those without lipodystrophy (31). Decreased production of adiponectin in lipotrophic adipose tissue has been proposed to be a possible cause of insulin resistance and higher triglyceride levels (31). Whether adiponectin is associated with osteonecrosis remains unknown. However, since hypertriglyceridemia had been suggested to be a risk factor of osteonecrosis (1), adiponectin might play an indirect role in the development of osteonecrosis.

The clinical course of HIV-related osteonecrosis is highly variable. In one recent study, more than half of the patients remained clinically stable while one-third worsened (6). In comparison with asymptomatic patients, a more rapid progression to total hip replacement in symptomatic patients was observed (15). Half of the patients with hip involvement required joint replacement at 2 years after the first osteonecrosis episode (6). In a follow-up study of 339 patients, 59% of 22 symptomatic patients underwent total hip replacement at a median of 10 months after diagnosis (15), especially those involving more than 50% of the hip joint (15). The majority of patients that did not undergo operation had persistent pain requiring long-term analgesics, and functional limitation was reported in 78% of them. Neither resolution nor improvement was found on MRI (15).

Allison et al. proposed an algorithm for evaluation and management of osteonecrosis in HIV-infected patients (7). Currently, the treatment of osteonecrosis is based on symptom relief (26). Although beneficial effect has been demonstrated in HIV-uninfected patients with osteonecrosis receiving bisphosphonate therapy (14), its effectiveness in HIV-infected patients remains to be studied. Generally, the orthopedic procedure is found to be safe for these patients (6). In a 2.3-year follow-up of 40 HIV patients with osteonecrosis who underwent surgical intervention, all patients retained well-functioning arthroplastic hips except for one case of staphylococcal infection, which was related to the patient’s persistent intravenous drug abuse (32).

There are several limitations in our study. The incidence rate of osteonecrosis was underestimated because osteonecrosis was diagnosed only in patients with joint symptoms for which MRI was performed. The small case number of patients with osteonecrosis precluded us from performing multivariate analysis to exclude possible confounders or identify interactions. Some risk factors, including antiphospholipid antibodies, were lacking in most cases in this retrospective analysis.

In conclusion, the incidence of osteonecrosis remains low in ethnic Chinese patients with HIV infection who have had prolonged exposure to HAART. The presence of lipodystrophy, a clinical clue of prolonged HAART exposure and HIV infection, may serve as a potential marker for early workup for osteonecrosis in symptomatic patients.

REFERENCES