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SHORT COMMUNICATION

Osteonecrosis in human immunodeficiency virus (HIV)-infected patients: a multicentric case–control study

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Abstract Osteonecrosis (ON) is a rare disabling complication occurring in patients with human immunodeficiency virus (HIV) infection at a higher frequency than in the general population despite effective combination antiretroviral therapy being made available, as recently documented by several retrospective studies. We designed a multicentric case–control study among HIV-infected patients cared for at institutions in the Italian CISAI group (Italian Study Group for Adverse Events in HIV Infection) to search for additional predictors of ON in this special population. All centers which observed at least one case of ON were requested to report data for central re-evaluation. Parallel HIV-positive, ON-free controls were randomly selected and matched with confirmed cases of ON for sex, age and CD4 T-cell counts at the time of HIV diagnosis. Fifteen cases and controls were included in the final sample. Univariate statistical analyses revealed a significant association between ON and exposure to steroids ($P = 0.001$), exposure to one or more drugs in addition to HAART (Highly Active Anti-Retroviral Therapy) ($P = 0.03$), high titers of total serum IgE ($P = 0.02$), loss of working ability ($P = 0.03$), triglycerides levels over 200 mg/dL before antiretrovirals ($P = 0.03$) and cholesterol levels over 200 mg/dL before and after antiretrovirals ($P = 0.03$ and 0.05, respectively). High serum IgE levels and loss of working ability in advance of ON appeared for the first time as possible predictors of ON in HIV patients, while long-term exposure to steroids, combined hyperlipemia and chronic treatment with other drugs in addition to antiretrovirals were confirmed. Predicting and preventing ON in the individual HIV-infected patient is therefore a clinically challenging opportunity.

Keywords Osteonecrosis · HIV · IgE · Dyslipidemia · Loss of working ability

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Introduction

Treatment of human immunodeficiency virus (HIV) infection improved significantly after the introduction of HAART (Highly Active Anti Retroviral Therapy), with a major increase in patient survival [1, 2]. As a consequence of longer treatment courses, occurrence of HAART-related

dysmetabolic events increased in parallel [1, 2]. Among these, osteonecrosis (ON) was documented by several retrospective studies using large cohort databases, showing that hip, knee and shoulder are the most frequently involved sites, bilaterally in a remarkable proportion of cases [3–13]. In a Bethesda cohort study, the incidence of ON was prospectively investigated and measured at 0.65 cases per 100 person-years, while the overall prevalence, calculated including cases tracked by magnetic resonance imaging (MRI) among asymptomatic carriers, was as high as 4.4% [4, 9]. Therefore, ON is a rare but clinically relevant and sometimes disabling condition affecting patients with HIV infection even in the HAART era. A better knowledge of predictors of ON in this setting may be useful to help prevention efforts [4–13]. The most frequently reported risk factors so far associated with ON are cigarette smoking, hyperlipemia, lipodystrophy, long-term use of steroids, presence of anti-phospholipid and anti-cardiolipin antibodies, alcohol abuse, as well as the duration of both HIV infection and antiretroviral therapy [4–13]. To search for additional predictors of ON, we designed a multicentric case–control study among HIV-infected patients cared for at institutions in the CISAI group (Italian Study Group for Adverse Events in HIV Infection). Clinical features and possible predictors of ON were compared in reported cases and site-matched controls.

Materials and methods

The steering committee of the CISAI group launched the study proposal early in 2009. All centers who could report on at least one case of ON since 2000 were requested to review the relative clinical records. Diagnosis of ON was confirmed when the findings of standard bone Rx scans of the clinically involved skeletal segment(s) were supported either by a concordant bone scintigram or by CT/MRI scans, or by both [5, 14]. Each contributing center was requested to provide an equal number of parallel HIV-positive, ON-free controls, randomly selected from all HIV-assisted patients after matching for sex, age and CD4 T-cell counts at the time of HIV diagnosis. For each case and control, the following parameters were requested: HIV viremia and CD4 T-cell counts both at the beginning of HAART and at the time of ON diagnosis (for controls, after an equal length of time during HAART as in the matched case); year of first HIV-positive test; type and duration of HAART regimen(s); exposure to at least a 14-day steroid course, prescribed for any reason up to 6 months in advance of ON diagnosis; type and number of additional medications prescribed at the time of ON; diagnosis of any AIDS-defining condition; co-infection with tuberculosis; history of alcohol and/or drug abuse; familial risk for cardiovascular diseases; smoking habits; presence of HAART-induced lipodystrophy of any type; current working status; current body mass index (BMI); fasting serum cholesterol, triglycerides and glucose both at the start of current HAART regimen and at ON diagnosis; presence of anti-phospholipid and/or anti-cardiolipin autoantibodies; total serum IgE levels; and plasma homocysteine. Whenever feasible, bone mineral density evaluations were requested for both cases and controls, both by standard DEXA scanning [15] and by quantitative ultrasound assays [16]. Duration and treatment of pain were recorded for all cases. The grade of ON-induced skeletal lesions was classified in accordance with Ficat and Arlet for hip and knee ON [17, 18]. Significance of statistical differences among groups was evaluated by the chi-squared test.

Results

Twenty-three sites were proposed to take part in this retrospective case−control study. Nine of these declined the invitation because of inaccessibility of medical records and/or lack of appropriate systems to retrieve cases diagnosed as ON. Seven additional sites did not contribute a case because of reported lack of diagnosis in the observational period. Twenty-six patients followed at seven CISAI group centers were referred with a proposed diagnosis of ON. However, eleven of these were excluded either because the diagnosis was not confirmed as described in the methods, or because of lack of relevant requested clinical or laboratory information. Fifteen patients from 4 centers (Como, Genoa, Perugia and Pescara) with a confirmed diagnosis of ON were included in the final sample, together with 15 parallel controls matched as described in the methods. All patients had presented with long-lasting localized pain except one, who was diagnosed with ON after a secondary bone fracture involving the femur head at the affected hip. Nine patients had ON of the hip, bilateral in 5 cases; 4 additional patients had ON of the knee, bilateral in 2 cases; and in the remaining 2 patients, ON involved the left shoulder in one case and both one shoulder and the right hip in the other case. Fourteen patients were classified as stage 1–3 of the Ficat classification, while 1 patient with bilateral hip involvement quickly progressed to grades 3 and 4. Conservative management was sufficient in all patients with low-grade lesions, whose pain subsided under supportive therapy with non-steroidal anti-inflammatory drugs after a mean of 4.3 ± 4.2 weeks. In the patient with grade 4 lesions bilateral hip replacement was safely performed in 2 stages, 2 and 3 years respectively, after ON diagnosis. As shown in Table 1, 12 (80.0%) patients were male, mean age 39.9 ± 5.9 years (range 31–53), mean BMI 24.1 ± 6.1

(range 18.2–41.4). The lowest CD4 T-cell counts were 89.5 ± 96.0/mm^3 (range 4–362), mean duration of HIV infection at diagnosis of ON was 11.4 ± 5.4 years (range 3–22); mean duration of HAART at diagnosis of ON was 38.2 ± 40.5 months (range 2–120). Mean cumulative dose of steroids was 2502.3 ± 3336.8 mg prednisone for the 11 patients in the ON group treated with steroids; none of them were treated with pulse therapy. Exposure to steroids occurred at a mean of 26.7 ± 35.7 months (range 1–120) before diagnosis of ON; mean duration of therapy with steroids was 79.0 ± 140.8 days (range 20–517). Total serum IgE levels were measured in 12 patients, 2.9 ± 1.9 months (range 1–6) in advance of the diagnosis of ON. Three patients experienced other cardiovascular manifestations: 2 of them suffered *ictus cerebri*, one during primary cerebral lymphoma, the other during acute neurotoxoplasmosis, both at the presentation of HIV disease; the third patient developed peripheral atherosclerosis and *claudicatio intermittens* in advance of ON. Twelve of the 15 patients had lost their working ability in advance of the onset of ON, because of: major psychiatric disorder (5 cases), hemiplegia due to brain lesions (3 cases), severe obesity (2 cases), articular grip (1 case) and HIV wasting (1 case).

Univariate statistical analyses revealed a significant association between ON and exposure to steroids ($P = 0.001$), exposure to one or more drugs in addition to HAART ($P = 0.03$), high titers of total serum IgE ($P = 0.02$), loss of working ability ($P = 0.03$), triglycerides levels over 200 mg/dL before HAART ($P = 0.03$),

Table 1 Demographic, clinical and immunological data for cases and controls

Variables	Cases, $n = 15$ (%)	Controls, $n = 15$ (%)	P value
Gender			
Males	12 (80.0)	11 (73.3)	0.7
Age (mean, years)	39.9 ± 5.9 (r. 31–53)	39.8 ± 4.1 (r. 33–51)	0.9
Race			
Caucasian	11 (73.3)	15 (100)	0.1
Black/Hispanic	4 (26.7)	0	
Risk factor			
Drug addiction	7 (46.7)	6 (40.0)	0.7
Heterosexual	5 (33.3)	4 (26.7)	
Homosexual	3 (20.0)	5 (33.3)	
Body mass index (kg/m^2)	24.1 ± 6.1 (r. 18.2–41.4)	23.6 ± 3.8 (r. 17.9–30.4)	0.8
CD4 T-cell count minimum (mean, cell/mmc)	89.5 ± 96.0 (r. 4–362)	109.3 ± 82.8 (r. 23–300)	0.5
Cigarette smoking	12 (80.0)	10 (66.7)	0.4
AIDS	12 (80.0)	10 (66.7)	0.4
TBC co-infection	3 (20.0)	2 (13.3)	0.6
Low socioeconomic status	11 (61.1)	7 (46.7)	0.1
HAART line			
1	9	10	0.9
2	3	3	
3	3	2	
HAART duration (mean, months)	38.2 ± 40.5	46.9 ± 35.1	0.6
ΔCD4 T-cell counts (mean, cell/mmc)[a]	427.9 ± 439.9	210.6 ± 150.1	0.07
Familial cardiovascular risk	1 (6.7)	2 (13.3)	0.5
Triglycerides after HAART > 200 mg/dL	9 (69.2)	4 (30.8)	0.06
Co-morbidity	10 (66.7)	5 (33.3)	0.07
Other drugs in addition to HAART	12 (80.0)	6 (40.0)	0.03
Long-term steroids	11 (73.3)	2 (13.3)	0.001
Loss of working ability	12 (80.0)	6 (40.0)	0.03
Cholesterol at baseline > 200 mg/dL	7/14 (50.0)	2 (13.3)	0.03
Triglycerides at baseline > 200 mg/dL	7/14 (50.0)	2 (13.3)	0.03
Cholesterol after HAART > 200 mg/dL	7 (46.7)	2 (13.3)	0.05
Serum level of IgE > 100 UI/mL	11/13 (84.6)	6 (40.0)	0.02

[a] Difference between minimum CD4 T-cell counts and CD4 T-cell counts at diagnosis of ON or after the same duration of HAART for controls

and cholesterol levels over 200 mg/dL before and after HAART ($P = 0.03$ and 0.05, respectively, Table 1). The presence of co-morbidities and serum levels of triglycerides over 200 mg/dL at ON diagnosis were near-significantly associated ($P = 0.07$ and 0.06, respectively, Table 1). Cigarette smoking, AIDS diagnosis, co-infection with tuberculosis, CD4 T-lymphocyte boosting and familial risk for cardiovascular disease were not associated with ON (Table 1).

Discussion

Our case–control multicentric study on predictors of ON was conducted on a relatively small sample of well-characterized cases and accurately matched controls from parallel HIV patients with similar clinical features (sex, age and CD4 T-cell counts at the time of HIV diagnosis). The patients were mostly young males, aged less than 50 years, providing evidence that hip, knee and shoulder are the most frequently affected sites, often bilaterally [5–13, 18, 19]. Our observation, based on an experimental design aimed at exploring predisposing factors other than HIV infection, its duration, its consequent immune imbalance and duration of antiretroviral therapy (all of which were well matched among cases and controls), confirms the multifactorial etiology of ON in this setting [5–13]. Indeed, more contributing factors than previously known were significantly associated with ON in our study [5–13].

Among already known factors, the association between ON and long-term exposure to steroids was confirmed. In our series, the patients were exposed for several reasons to high doses of steroids for protracted time intervals, ranging from 2 to 17 months. A remarkably high dose of steroids was administered to 11 of the 15 patients with ON in our series, none of whom received an initial pulse dose; only 2 controls received steroids on comparable time frames. A high initial cumulative dose of steroids and their administration for a long period (2–78 months in advance of ON) was associated with ON in other settings [19]. Steroids play an important role in modifying bone metabolism, causing fat infiltration of bone marrow, marrow stem cells differentiation into adipocytes, and a consequent increase of the intraosseous pressure, which may, in turn, decrease blood flow into small vessels causing obstruction [5, 19]. Steroids may also induce fat embolization of small vessels through secondary hyperlipemia [5, 19]. Interestingly, higher cholesterol and triglyceride serum levels were also associated with ON in our sample.

Hyperlipemia is a well-established consequence of both HIV infection and most HAART regimens; its involvement in atherogenic and thromboembolic pathways is so well characterized that its significant association with ON in the present setting does not deserve any further discussion [1, 2, 5].

To our knowledge, this is the first time that ON has been significantly associated with higher total levels of serum IgE, which may be plausibly linked to the multifactorial pathogenesis of ON in HIV infection. High levels of IgE were associated with high levels of Th2-type cytokines (IL4, IL6 and TNFα) in HIV patients, more frequently in those with advanced disease [20, 21]. Higher levels of serum IgE and Th2-type cytokines have been associated with a possibly relevant role in the process of atheromasic plaque destabilization and rupture, as well as in ischemic and thrombotic events in settings other than HIV infection, such as instable angina, acute myocardial infarction, pulmonary embolism and cerebral infarction [22–28]. Furthermore, high IgE levels may promote platelet activation through the binding of FcεRI (high-affinity IgE receptor) and FcεRII (low-affinity IgE receptor) surface membrane receptors, thus inducing a well-characterized cascade of events, including thrombin activation and thrombin-antithrombin III complex formation, ultimately leading to intravascular thrombi and/or emboli [29]. This may well be the case in ON, which has frequently been reported as multifocal both in HIV patients, including the present series, and in other settings [5–13, 18, 19]. Interestingly, higher levels of IgE have been reported in advance of acute vascular events, followed by lower or near normal levels in the post-acute phase, suggesting a trapping of the immune trigger inside thrombi [24, 26]. This was also the case in 4 of our patients for whom follow-up values were available (data not shown). Finally, higher IgE levels were more often documented in males in the general population, which may partly explain the frequent occurrence of ON in male HIV-infected patients, as in the present series, and in other reports [4, 6, 8, 10, 12, 24].

Another novel finding from our dataset was that the loss of working activity in advance of ON was significantly more frequent among cases than controls. Cardiovascular diseases have been related with loss of physical activity and protracted hypokinetic states [30]. Conversely, several lines of evidence support the fact that adequate physical activity may significantly reduce the risk of thrombotic and embolic events [30, 31]. It is plausible, therefore, to consider this novel association as one bearing interesting biological potential as to the unraveling of the multifactorial pathogenesis of ON.

A remarkable proportion of patients in our series (12/15) took several other drugs in addition to HAART for different comorbid conditions at the time of ON. In particular, 4 were taking steroids, 6 were taking long-term cotrimoxazole, 5 were taking antipsychotic and/or antidepressant drugs, and 4 were taking antihypertensive and/or lipid lowering drugs. Many of these drugs may have played a

contributing role on endothelial dysfunction, in conjunction with antiretroviral treatment [32].

Finally, several studies reported on the association between ON and cigarette smoking. In our sample, most of the HIV patients were smokers both among cases and controls (12 and 10, respectively), in line with many other reports on HIV-infected patients [5–8]. As a consequence, the role of smoking on the occurrence of ON simply could not be addressed by our study design.

A major limitation of our study was that we could not explore the potential role of HIV itself and antiretroviral therapy in the pathogenesis of ON. Several lines of evidence recently documented that HIV may exert a direct role in endothelial activation and dysfunction [2, 33]. Similarly, long-term administration of HAART has been documented as a potential cause of vascular events in HIV-infected patients [2, 33]. These limitations, however, did not apparently hamper our attempt to envisage novel possible factors contributing to the pathogenesis of ON. In addition, the limited size of our sample did not allow us to verify the independent nature of each association with ON using a multivariate model. So our findings should be considered with caution until further confirmation.

In conclusion, patients at higher risk of developing ON in our sample shared multiple concomitant features: long-term exposure to steroids, combined hyperlipemia, high levels of total serum IgE, loss of working ability in advance of ON, chronic treatment with other drugs in addition to HAART, as well as a higher level of total serum IgE levels, demonstrated here for the first time. Our findings may help to estimate the risk of ON in the individual HIV-infected patient. The novel associations demonstrated in this study deserve further validation with other experimental designs.

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