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AIDS 2007, **21**:2251–2256

Kaposi's sarcoma in HIV-infected patients: when and how should we evaluate bone involvement?

Kaposi's sarcoma (KS) was first described in 1872 [1]. In HIV patients, KS is an AIDS-defining malignancy and mainly involves the skin. KS of the bone and skeletal muscle are rare and often asymptomatic [2–4]. It has even been suggested that the presence of bone lesions assists in the differentiation of bacillary angiomatosis from AIDS-related KS, which has similar cutaneous abnormalities but not usually bone lesions [5]. Here we report the case of an HIV-infected patient with osseous KS.

A 37-year-old HIV-infected homosexual man was admitted to our unit in October 2006 because of a 10 kg weight loss and extensive cutaneous KS lesions. HIV disease had been diagnosed in March 2003, when cutaneous KS lesions developed on his legs. At that time the CD4 cell count was 163 cells/ μ l, and the HIV viral load was 31 622 copies/ml. The patient was initiated on a combination antiretroviral therapy with efavirenz, lamivudine, and didanosine, which resulted in a partial response but did not resolve the cutaneous KS lesions, probably partly as a result of poor compliance with the treatment. In July 2006, the patient decided to stop his antiretroviral therapy. At admission in our unit, physical examination revealed an afebrile patient and the presence of new KS cutaneous lesions on his legs. Standard laboratory tests and in particular a full blood count and the C-reactive protein level were normal. The CD4 cell count was 190 cells/ μ l, and the HIV viral load was 16 681 copies/ml. An upper digestive fibroscopy, a colonoscopy, and chest and abdominal computed tomography (CT) scans were performed in a search for visceral KS. We found no lesions in the lungs, gastrointestinal tract, spleen, or liver. The abdominal CT scan, however, showed a para-aortic tumour and multiple osteolytic vertebral lesions with cortical disruption of the T11, T12 and L1 vertebrae, with no involvement of the overlying skin. Magnetic resonance imaging of the spine showed many more osteolytic vertebral lesions, extended from T10 to L5. These lesions emitted a hyperintense signal on short tau inversion recovery sequences and a hypointense signal on T1-weighted sequences, with an intense enhancement after contrast injection (Fig. 1). The spinal cord was normal. The technetium-99m-methylene diphosphonate scan showed increased uptake activity in areas corresponding to the CT scan abnormalities. The gallium-67 scan was normal. CT-guided core needle biopsy of a vertebral lesion led to an immunohistological diagnosis of KS, characterized by a massive infiltration of proliferating spindle-shaped cells, aggregates of newly

formed blood vessels, and reactivity against anti-CD34, anti-CD31 and anti-human herpesvirus 8 antibodies. Retrospectively, after disclosure of the radiological findings, the patient reported mild localized back pain but only when he was questioned on the subject. The patient was treated with liposomal doxorubicin administered intravenously every 2 weeks. After 6 months of chemotherapy, the patient improved clinically, but there were no radiological changes.

KS is a multisystem and multicentric disease attributed to human herpesvirus 8 [6]. It primarily affects the skin and mucosa. Musculoskeletal KS lesions are rare, but they may also occur, mostly combined with aggressive cutaneous or mucosal KS lesions [2]. KS bone involvement develops either as a direct extension of an extensive overlying cutaneous disease or extensive lymph node lesion, or as part of a metastatic process. In a recent review of the medical literature, Caponetti and coworkers [2] identified reports concerning 66 patients with KS of the musculoskeletal system, 28 of whom had HIV infection. Bone lesions in these HIV-infected patients, as in the patient we report here, were mainly located on the axial skeleton; thus 11 of the 28 HIV-infected patients had vertebral lesions [2].

Bone KS lesions, especially of the vertebrae, may lead to spinal cord compression and neurological sequelae [7,8]. Early diagnosis of these lesions followed by systemic chemotherapy regimens and combination antiretroviral therapy are therefore essential because they may prevent the occurrence of neurological sequelae. Radiation therapy may be performed to relieve bone pain. We first suggest that patients with KS, especially those with aggressive widespread disease, should be carefully asked about bone pain. Although bone involvement in KS patients has rarely been found to be asymptomatic, bone pain is usually mild and may not be reported spontaneously [2]. In patients with bone pain a meticulous evaluation for osseous lesions should be performed using CT scans and magnetic resonance imaging. X-rays are not sensitive enough to detect osseous lesions. In addition, we would stress the fact that the presence of cutaneous abnormalities and bone lesions in HIV-infected patients should not only suggest a diagnosis of bacillary angiomatosis, but also KS with bone involvement [5]. To distinguish bacillary angiomatosis from KS, it is essential to obtain tissue for histological analysis and culture.

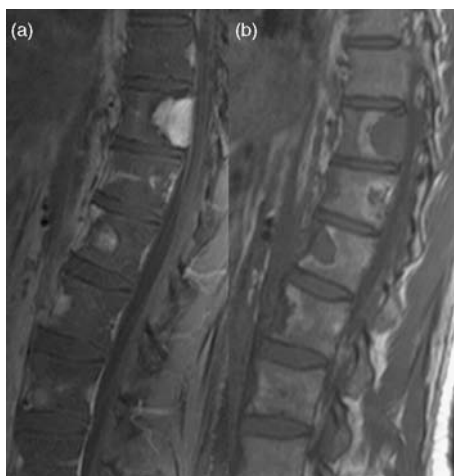


Fig. 1. Sagittal T1-weighted images of the patient's spine. (a) At the thoraco-lumbar junction: multiple vertebral lesions with perilesional fatty halo. (b) Fat-saturated contrast-enhanced image: marked enhancement of the lesions.

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Received: 24 June 2007; accepted: 9 July 2007.

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A truvada hypersensitivity reaction simulating abacavir hypersensitivity

Hypersensitivity reactions to abacavir occur in approximately 5% of treated individuals, and may be manifested by fever, rash, constitutional complaints, gastrointestinal disturbances and hematological abnormalities [1]. These reactions can be life-threatening particularly if patients are re-challenged with abacavir [2]. The presence of HLA-B*5701 has been associated with a higher risk of abacavir hypersensitivity reactions in Caucasian and Hispanic populations [3,4]. To date, no other nucleoside reverse transcriptase inhibitors have been reported to cause similar hypersensitivity reactions. We report a case of an emtricitabine/tenofovir hypersensitivity reaction.

An 18-year-old African American man with a CD4 cell count of 322 cells/ μ l and an HIV-1-RNA viral load of 4550 copies/ml was admitted to the hospital with a 2-day history of fevers to 103.6°F, fatigue, myalgias, conjunctival infection and non-bloody diarrhea. He denied nausea or vomiting but had a poor appetite over this time. Ten days previously, he had entered a randomized clinical trial for antiretroviral-naïve patients. He initiated open-label treatment efavirenz and blinded treatment with emtricitabine/tenofovir (or placebo) or abacavir/lamivudine (or placebo).

The patient's physical examination revealed a temperature of 102.2°F and orthostatic hypotension. His

laboratory findings were significant for an elevated white blood cell count of 17 000 cells/ μ l, blood urea nitrogen level of 23 mg/dl, and creatinine level of 1.4 mg/dl. Intravenous fluids and broad-spectrum antibiotics were administered. HIV medications were withheld. Blood, urine and stool cultures were negative, and a computed tomography scan of the abdomen and pelvis was normal. The patient recovered and went home after 4 days with suspected bacterial gastroenteritis on ciprofloxacin and metronidazole.

The patient returned to the study unit the day after discharge and received his study medications under direct observation. Within one hour, he complained of a headache and numbness of his hands and feet. He then had projectile vomiting and was subsequently found to have a systolic blood pressure of 70 mmHg and a heart rate of 140 beats a minute. Physical examination showed early desquamation of his scalp and face.

The patient was transferred to the medical intensive care unit where he received intravenous fluids and brief hemodynamic support with vasopressors. All cultures remained negative. HIV medications were withheld, and he recovered after 4 days. The patient was diagnosed

clinically with an abacavir hypersensitivity reaction. The unblinding process revealed that he had been randomly selected to receive emtricitabine/tenofovir. Mass spectroscopy of the dispensed medications confirmed that the patient's pills indeed contained emtricitabine/tenofovir. The patient was subsequently given zidovudine/lamivudine and efavirenz without further problems.

Abacavir hypersensitivity is a potentially fatal syndrome with a multisystemic presentation [1]. Our patient presented within 10 days of initiation of his medications and exhibited many features similar to those reported with abacavir hypersensitivity, including fever, myalgias, fatigue, diarrhea, rash and hypotension. His symptoms resolved rapidly after discontinuing the medications and became much more severe upon rechallenge. The initial assessment by the caring physicians was that he had an acute febrile illness, probably viral or bacterial in origin, and that it would be safe to resume his antiretroviral therapy.

We believe this is one of the first reports of a systemic emtricitabine/tenofovir hypersensitivity reaction. We cannot discern which drug might have induced this reaction. The patient was successfully given lamivudine subsequently, which is chemically similar to emtricitabine [5]. In a recent research letter, Lockhart described nine patients with suspected tenofovir cutaneous hypersensitivity reactions, all manifesting as maculopapular or vesicular rashes [6]. Only one of their patients appeared to have a more systemic illness that included urticaria, shortness of breath, and angioedema. Our patient did not present with either a maculopapular or vesicular rash, but did have desquamation of his scalp and face. He had more of a systemic illness that involved gastrointestinal symptoms, fever, and hypotension, similar to the reaction seen with abacavir hypersensitivity. We thus suspect that this patient had a systemic reaction to tenofovir.

Clinicians should consider hypersensitivity reactions in patients taking nucleoside or nucleotide reverse transcriptase inhibitors who present with a systemic illness. Hypersensitivity reactions similar to those described with abacavir may occur with other nucleoside reverse transcriptase inhibitors. It may be prudent to hold these medications upon presentation and exercise caution with rechallenge.

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Sponsorship: This work was supported by ACTG training grant U01069513-01.

Conflicts of interest: C.J.F. has received honoraria and research grants from Gilead Sciences, Inc.

Received: 4 July 2007; accepted: 16 July 2007.

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Lack of anti-HIV activity of entecavir in an HIV patient coinfecting with hepatitis B and delta viruses

Approximately 5–10% of individuals with HIV infection suffer from chronic hepatitis B. For co-infected patients needing antiretroviral therapy, the combination of tenofovir plus emtricitabine is currently the preferred option. In contrast, for individuals with elevated CD4 cell counts and no need for antiretroviral therapy, pegylated interferon has been advised for hepatitis B e antigen-positive chronic hepatitis B [1]. It is currently unclear what is the best option for hepatitis B e antigen-negative chronic hepatitis B when antiretroviral therapy is not needed. Concerns about the risk of selecting K65R in HIV, despite using only the approved anti-hepatitis B virus (HBV) dose of 10 mg per day adefovir, have precluded the open use of this drug in this population [2]. As entecavir was thought

to have potent and selective anti-HBV activity, it was considered the drug of choice for this subset of co-infected patients. A recent report has, however, challenged this view; a series of three patients who received entecavir without concomitant antiretroviral therapy showed a 1 log₁₀ decline in plasma HIV-RNA and emergence of the M184V mutation in one patient [3].

We have had the opportunity to examine a 43-year-old man with delta hepatitis and CD4 cell counts above 350 cells/μl in whom entecavir 1 mg/day was prescribed in an attempt to ameliorate liver disease, taking into account preliminary findings suggesting that potent new anti-HBV nucleos(t)ide analogues might be of benefit

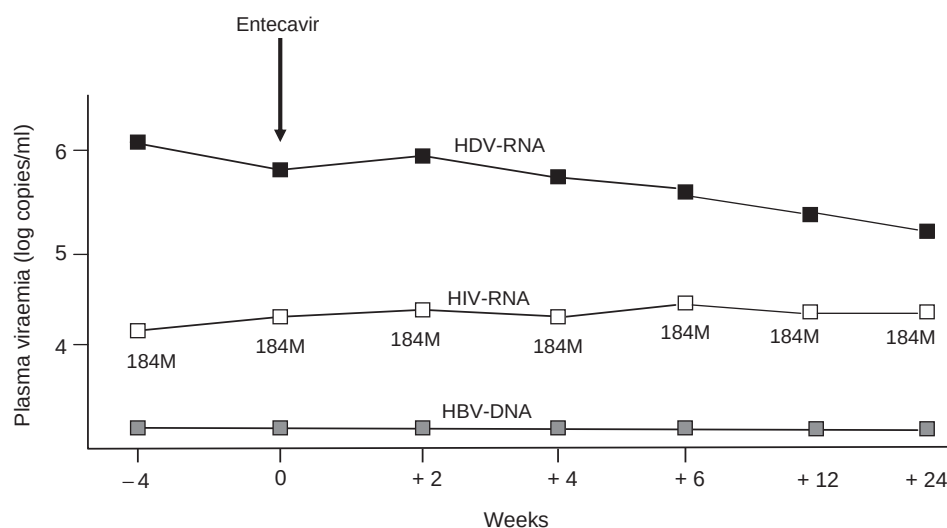


Fig. 1. Evolution of viral markers on entecavir. HBV, Hepatitis B virus; HDV, hepatitis D virus.

against delta virus. He had recently been diagnosed with liver cirrhosis and had persistently elevated aminotransferases. Serum HBV-DNA had been repeatedly undetectable (<15 IU/ml) probably as a result of the suppressive interference of delta virus on HBV replication. Plasma HIV-RNA levels had been in the range of 20 000 copies/ml for the past year. Figure 1 shows the virological outcome in this patient after introducing entecavir. No significant changes in plasma HIV RNA nor the selection of M184V occurred in five consecutive specimens taken during the first 24 weeks of therapy.

Our results argue against a direct anti-HIV activity of entecavir in this type of co-infected individual. Declines in HIV viraemia after the introduction of acyclovir [4] or valacyclovir [5] have already been reported and explained by an indirect effect on HIV replication after the suppression of herpes simplex virus replication. We hypothesize that the suppression of HBV replication in our patient as a result of delta superinfection precluded the recognition of any indirect beneficial effect of entecavir on HIV replication. Entecavir may thus be a good alternative option for treating chronic hepatitis B in HIV-infected individuals in no need of antiretroviral therapy.

Acknowledgements

The authors wish to thank Angelica Corral for excellent laboratory technical assistance and Raymond Schinazi for his helpful comments.

Large lymphadenopathies complicating the abacavir hypersensitivity reaction

Abacavir is a nucleoside analogue approved for the treatment of HIV infection, which may cause hypersensitivity reactions within the first 4–6 weeks of therapy

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Sponsorship: This work was partly supported by grants from Fundacion Investigacion y Educacion en SIDA (IES), the European VIRGIL and NEAT networks, and Red de Investigación en SIDA del FIS (ISCIII-RETIC RD06/006).

Conflicts of interest: None.

Received: 19 July 2007; **accepted:** 30 July 2007.

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in approximately 5% of cases [1]. Typically, clinical manifestations include fever, rash, malaise, respiratory and gastrointestinal symptoms. Herein, we report three

individuals who developed large lymphadenopathies after the initiation of abacavir-containing regimens, mimicking immune reconstitution inflammatory syndrome (IRIS).

Three Caucasian men infected with HIV were admitted to two hospitals located in Madrid complaining of painful neck enlargement, along with fever, rash and severe malaise. The CD4 cell counts were below 350 cells/ μ l in two of them and all had plasma HIV-RNA levels above 1000 copies/ μ l (Table 1). All but one had started their first antiretroviral therapy 6–7 days earlier with distinct abacavir-containing antiretroviral regimens. The third patient had already been on antiretroviral therapy and had experienced a doubtful abacavir hypersensitivity reaction with fever and malaise 12 months earlier in another hospital after exposure for only 3 days to abacavir, which was discontinued. Currently, he had begun a regimen with abacavir, lamivudine and atazanavir/ritonavir before presenting 5 days later with a large neck and axilar lymphadenopathies.

Although painful lymph node enlargement was the main reason for complaining in all three patients, mimicking IRIS, all patients presented with fever and rash. Although they had been advised to stop abacavir in case these symptoms developed, they continued on the drug until painful lymphadenopathies appeared. Physical examination revealed large cervical and axilar lymphadenopathies in all cases. Laboratory values showed liver enzyme elevations and leukocytosis. All antiretroviral agents were discontinued and intravenous fluids and corticosteroids were given. The first two patients completely recovered after 3–5 days. The patient who had been rechallenged with abacavir recovered from lymphadenopathies within 5 days but developed multiorgan failure that required admission to the intensive care unit. Eventually he completely recovered over the next 3 weeks. All patients were retrospectively tested for HLA-B*5701 and were found to be positive.

Drug hypersensitivity is the major limiting side effect of abacavir therapy. It must be considered in all HIV-infected individuals presenting with suggestive clinical signs or symptoms within the first 4–6 weeks of abacavir therapy. Resolution is the rule within 72 h after drug withdrawal. Characteristic manifestations include fever, rash, fatigue, respiratory or gastrointestinal symptoms. The persistent use of abacavir despite initial manifestations or unrecognized hypersensitivity reactions may result in the development of severe clinical illness comprising lethargy, generalized oedemas and respiratory insufficiency. Anaphylaxis will evolve to hepatic and renal failure, hypotension, and eventually death [2]. Laboratory abnormalities may include changes in liver function tests, and increases in creatine phosphokinase, lactate dehydrogenase and creatinine.

Table 1. Main characteristics of the study population.

No.	Sex	Age (years)	Race	CD4 cell count (cells/ μ l)	HIV-RNA level (copies/ml)	Drugs	HLA B*5701	Days with abacavir to HSR	Clinical manifestations	Days to recovery after stopping abacavir
1	Male	36	Caucasian	300	3162	ABC, 3TC, LPV/r	Positive	7	Fever, rash, lymphadenopathies	4
2	Male	27	Caucasian	159	55 000	ABC, ZDV, 3TC, CMX	Positive	6	Fever, rash, lymphadenopathies	4
3	Male	58	Caucasian	1360	52 653	ABC, 3TC, ATV/r	Positive	5	Fever, rash, lymphadenopathies, multiorgan failure	20

ABC, Abacavir; ATV/r, atazanavir boosted with ritonavir; CMX, cotrimoxazole; HSR, hypersensitivity reaction; LPV/r, lopinavir boosted with ritonavir; 3TC, lamivudine; ZDV, zidovudine.

Drug hypersensitivity reactions accompanied by lymph node enlargements have already been reported in association with allergic reactions to penicillin, cephalosporines, sulfonamides, carbamazepine and phenytoin [3]. To the best of our knowledge, this is the first report of lymphadenopathies as part of the abacavir-associated hypersensitivity reaction, probably because patients are generally advised to stop the medication as soon as the first hypersensitivity reaction manifestations appear.

The suspicion of IRIS may challenge the recognition of abacavir-associated hypersensitivity reaction when lymph node enlargement is the main clinical manifestation, as it was in our cases. Large lymphadenopathies and dermatological manifestations may be recognised in up to one third of IRIS after the initiation of potent antiretroviral therapy [4]. The presence of severe immune deficiency and high viral load along with rapid CD4 cell gains after HAART initiation favours the diagnosis of IRIS. Corticoids may help to manage IRIS even without stopping HAART. In contrast, abacavir-associated hypersensitivity reaction may evolve to fatality if antiretroviral therapy is continued. The removal of abacavir and the positive testing for HLA-B*5701 clearly confirmed the diagnosis in our patients. The strong positive predictive value of abacavir-associated hypersensitivity reaction of the HLA-B*5701 allele has been well established in Caucasian and Hispanic individuals [5–9].

In conclusion, large lymphadenopathies mimicking an immune inflammatory reaction may develop in patients who start an abacavir-containing regimen and continue to receive the drug despite initial manifestations of hypersensitivity reaction. HLA-B*5701 testing may help to make the appropriate diagnosis.

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Conflicts of interest: None.

Received: 26 May 2007; *revised:* 29 June 2007; *accepted:* 10 July 2007.

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