Multifocal Bone Infarcts and Buprenorphine: Association or Coincidence?

To the Editor:

Bone infarcts result, probably, from interruption of bone blood flow due to intraosseous arterial thrombosis or hypertrophy of adipocytic cells[1]. Bone infarcts (denoted as multifocal when more than 5 sites are involved[2]) have recently been described in HIV-infected patients[3]. In this context, a relationship with intravenous drug use has been established by some authors[4]. Buprenorphine marketed under the trade name Subutex® is prescribed for opioid detoxification and subsequent maintenance therapy. It can be administered sublingually, subcutaneously, or intravenously. We describe 4 patients presenting with multifocal bone infarcts in whom buprenorphine abuse was detected.

Patient 1, a 36-year-old woman, never pregnant, was a former cocaine addict, but stated she had not taken the drug for 6 years. She had since been treated with oral buprenorphine (Subutex) daily. For 2 years, she had experienced day and night pain of the knees, ankles, and feet. Her alcohol consumption was one or 2 glasses per day. Magnetic resonance imaging (MRI) revealed multifocal infarcts of the distal femoral and proximal tibial extremities, the patellas, and both femoral heads.

Patient 2, a 34-year-old man, was hospitalized for pain of the hips, knees, and tibias. He admitted a tendency to heavy drinking, consuming as many as 6 cans of beer a day. He did not admit drug use (i.e., buprenorphine) although he stated he occasionally smoked hashish. Bone scintigraphy revealed increased uptake in the knees and femoral heads. MRI detected osteonecrosis of both hips and infarcts of the femoral condyles, the proximal extremities of the tibias, and some foot bones (calcaneus, talus; Figure 1A).

Patient 3, a 36-year-old man, presented with diffuse joint pain of over 3 years' duration. He was a former drug addict (heroin, cocaine, hashish) and was receiving treatment with oral buprenorphine (Subutex). His alcohol consumption was low and very intermittent. Hepatitis C had been treated by ribavirin and interferon 3 years earlier and viral load was undetectable. Radiographs showed advanced necrosis of both humeral heads, the distal extremity of the phalanx of the right great toe, and both hips. Radiographs of knees showed slightly heterogeneous trabecular bone, while MRI of these joints revealed bone infarcts extending to the distal femoral and proximal tibial extremities (Figure 1B).

Patient 4, a 35-year-old woman, never pregnant, sought medical advice for pain in both knees of 2 years' duration. She was a former heroin addict, treated with buprenorphine (Subutex) for more than 5 years. She did not drink alcohol. MRI revealed bone infarcts extending to the lower femoral and proximal tibial extremities. Hepatitis C antibody was positive, but tests for viral RNA were negative.

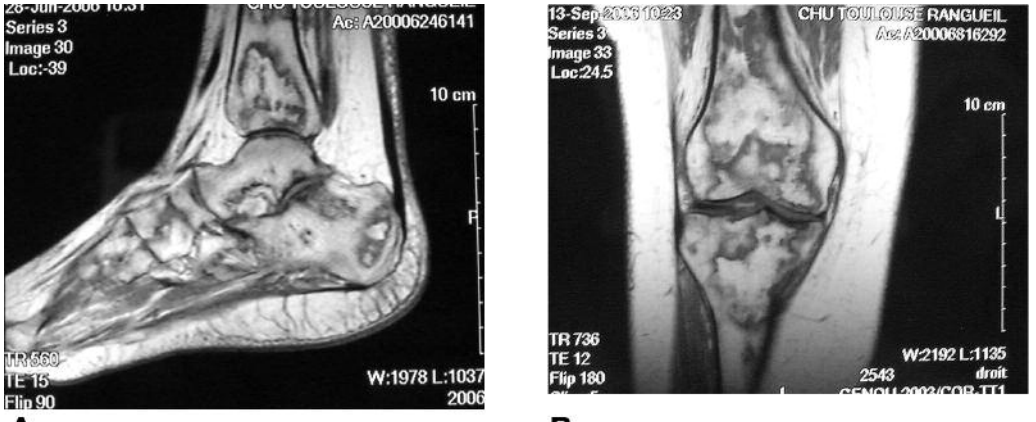
In all these patients, blood count, cholesterol and triglyceride levels, and liver function tests were normal. HIV serology was negative, as were tests for antinuclear, antiphospholipid, anti-ß$_2$-glycoprotein I, and anticryoglobulin antibodies and circulating anticoagulant (lupus anticoagulant). Coagulation was normal (prothrombin time, international normalized ratio, partial thromboplastin time). Blood and urine toxicology tests detected only buprenorphine.

Our patients presented avascular necrosis or bone infarcts at a mean of 6 sites. Buprenorphine was detected in all patients by urine toxicology tests. One patient admitted former alcohol abuse, but current laboratory findings showed no signs of continuing major alcohol consumption: there was no macrocytosis or abnormal liver finding.

Mont, *et al*[2] in 1999 studied 101 patients with multifocal osteonecrosis to determine the causes of the disorder. The 101 patients presented 630 necroses, which principally affected the hips (200), knees (179), shoulders (146), and ankles (71). Ninety-two of 101 patients had been treated with corticosteroids and 10 of 101 were former heavy drinkers. It was noteworthy that steroids had been administered for rather particular reasons: acute lupus erythematosus in 38 patients and kidney transplant in 15. Other reports have attributed multifocal bone infarcts to a variety of diseases: arterial disease of the lower limbs, acute disseminated lupus erythematosus, antiphospholipid syndrome, cytosteatonecrosis, Gaucher's disease, or sickle cell disease[5,6].

Several studies have demonstrated an abnormally high frequency of avascular necrosis in HIV carriers, about 100-fold higher than in a control population[3,7]. The osteonecrosis was often multifocal and secondary to corticosteroids, alcohol hyperlipidemia induced by protease inhibitors, antiphospholipid antibodies, and protein S deficiency. Matos, *et al*[4] found a statistical relation between intravenous drug use and osteonecrosis in HIV carriers.

The association of multifocal bone infarcts and buprenorphine has not previously been reported. Three of our patients had no other risk factors for multifocal necrosis. A priori, buprenorphine does not affect the vascular system or coagulation. Did our patients conceal intravenous use of buprenorphine? Could microemboli of poorly dissolved buprenorphine in the marrow cause infarcts? Neurologic or systemic embolic events after use of parenteral buprenorphine have been related[8,9]. Of course, a coincidence cannot be ruled out. However, we suggest that buprenorphine consumption should be investigated in evaluation of multifocal bone infarcts, especially if no other cause is found and if the clinical setting raises suspicion of drug abuse.



A B

Figure 1. A. Patient 2, MRI of the foot and ankle; T1-weighted sequence shows marrow necrosis of the distal extremity of the tibia, calcaneus, and talus. B. Patient 3, MRI of the right knee; T1-weighted sequence shows marrow necrosis of the femur and tibia.

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