Multifocal osteonecrosis and osteomyelitis in a liver transplant recipient

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ABSTRACT
Osteonecrosis is the destruction of bone as a result of temporary or permanent cessation of blood supply to the bones. Trauma, drugs, infections, hypercoagulability and solid organ transplantation are the most common causes. Osteonecrosis has been reported in many case series after renal, liver and cardiac transplantation; mainly in areas adjacent to the joints, especially on hip. Here, we are reporting multifocal osteonecrosis with osteomyelitis including diaphyseal region of the tibia in a patient with liver transplantation.

Keywords: Infection; liver transplantation; osteonecrosis.

CASE REPORT
A 42-year-old male patient, who underwent liver transplantation due to HBV-associated liver cirrhosis two years ago, was hospitalized on April 2013 with high grade fever, chills and abdominal pain. In his history, he had stenosis of biliary duct anastomosis and, percutaneous biliary cholangiography and balloon dilatation with internal drainage were performed four days ago. At the presentation, he was under methylprednisolone 8 mg/day, tacrolimus...
2 mg/day, entecavir 0.5 mg/day, ibandronic acid 150 mg/month and calcium 1000 mg/day. In addition he was on eltrombopag 50 mg/day therapy due to immune thrombocytopenia since 2011.

At admission to our clinic blood pressure was 125/75 mmHg, pulse was 96 bpm and temperature was 38.5 °C. Physical examination showed splenomegaly, abdominal tenderness and scleral icterus. Upon admission, acute phase reactants were elevated with a white blood cell count (WBC): 12,470/mm³ with raised neutrophils at 77%, C-reactive protein (CRP) 23 mg/dL. Blood chemistry showed cholestasis with alkaline phosphatase: 386 IU/L, gamma glutamyl transferase: 83 IU/L, total bilirubin: 1.57 mg/dL and direct bilirubin: 1.05 mg/dL. Hepatitis B surface antigen was negative. Sample from biliary fluid obtained from percutaneous stent was revealed that Klebsiella and Enterococcus microorganisms. Intravenous antibiotic therapy with cefoperazone/sulbactam 2 g, bid was started for cholangitis. This was followed up by a course of oral co-amoxiclav with ciprofloxacin following discharge.

On May 2013, he presented again with high grade fever and acute swelling on left knee and ankle with pain until 10 days prior to admission. His laboratory results were as follows; Hemoglobin: 9.7 g/dL, WBC: 8,340/mm³ with raised neutrophils at 76.3%, platelet: 21,000/mm³, CRP: 1.78 mg/dL, erythrocyte sedimentation rate (ESR): 27 mm/h. Blood chemistry showed normal hepatic and renal function. The antinuclear antibody, rheumatoid factor and anticardiolipin antibodies were negative. Effusions of the left knee and left ankle joint were aspirated. No organism was seen by using gram staining on the microscope and cultures for bacteria were found to be negative. Intravenous cefoperazone/sulbactam 2 g, bid was started again for cholangitis. This was followed up by a course of oral co-amoxiclav with ciprofloxacin following discharge.

Two months later the patient was admitted to the hospital due to worsening of his knee pain. Scintigraphy imaging was performed at that time. At whole body 99mTc-labeled hexamethylpropyleneamine oxime (99mTc-HMPAO) leukocyte scintigraphy, there were mildly increased osteoblastic activities at left proximal and distal tibia (Figure 2). In addition 99mTc-MDP three-phase bone scan images showed, increased soft tissue perfusion and activity at both perfusion and blood pool phases, in addition increased osteoblastic activity at bone phase on left knee and left ankle. These findings were compatible with inflammation and had been interpreted as infection. Due to uncontrolled bacterial infection; osteomyelitis was thought to be added over areas of osteonecrosis, during his follow-up.

DISCUSSION

The number of liver transplantations worldwide has increased dramatically over the past decade. Osteonecrosis associated with solid organ transplantation has been reported in many case series and, generally is localized at femoral head. Although the prevalence of ON after renal transplantation has been reported to be 5-24%,
relatively lower prevalence of ON is observed after liver transplantation 2-8.2%[1,4]. This difference may be explained in some way by the underlying metabolic problems associated with chronic renal failure.[1] The risk factors of ON in liver transplant recipients have been reported as osteoporosis, hypercoagulability, drugs especially corticosteroid therapy, smoking, alcohol abuse, trauma etc. However, association between age, Child score (in cirrhotic patients), biochemical parameters and ON have not been found.[1,3] In addition, decreased hip and knee ON incidence has reported in patients treated with cyclosporine and tacrolimus which might reflect the steroid sparing effect of these drugs.[6]

Drugs, especially steroid therapy are important risk factors of ON. The most commonly affected sites of ON in patients on steroid therapy are femoral and humeral heads.[8] In addition, knee joints, talus, lunate and scaphoid bones are susceptible to ischemic necrosis because of their geometry, nutritional characteristics and hemodynamic features. Also is not clear whether the risk of ON is related to cumulative corticosteroid dosage or not dose dependent.[1,8-12] In the literature, some case series showed that corticosteroid associated ON could be related to individual response (e.g., changes in steroid metabolism, hypercoagulable, hypofibrinolysis and genetic factors).[1,2] In contrast, many different investigators suggest that steroid-induced osteonecrosis is dose dependent.[1,11-13] In our liver transplantation center, steroid usually tapered in three to six months. However, our patient has a history of high dose steroid usage for a long time due to immune thrombocytopenia. Although liver transplantation is known as a risk factor of ON, high cumulative corticosteroid dosage may have contributed to ON in our case.

Osteopenia is another risk factor for ON.[14] On the other hand, prolonged therapy with bisphosphonates, adversely leads to ON of the jaws in some patients.[14] Bisphosphonates associated
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ON rarely occurs in the long bones, only one case was reported on zoledronic acid therapy.\textsuperscript{[15]} In a study, 20 cases of bisphosphonate-related osteonecrosis were reviewed and 16 alendronate and four ibandronate usage were reported.\textsuperscript{[14]} Our patient was using ibandronate for two years for osteoporosis, and this could be another triggering risk factor of ON.

Although there were some case reports regarding coexistence of avascular necrosis and osteomyelitis, we have not any concrete proof that one of these factors might be a risk factor for the other one. It is believed that there is an association between preexisting avascular necrosis and osteomyelitis. Patients with SLE, or HIV infection, or sickle cell disease, or solid organ transplantation are inclined to develop avascular necrosis because they might use steroid and increased risk factors for thrombosis.\textsuperscript{[16,17]} However, avascular necrosis is a risk factor for septic arthritis regardless of the underlying disorder.\textsuperscript{[18,19]} Septic arthritis has been reported to occur in during the follow-up osteonecrosis especially immunocompromised patient due to lupus or organ transplantation.\textsuperscript{[20-23]} On the other hand, in situations with bacteriemia, hematogenously distributed bacteria possessing the specific ability to bind to bone collagen and, has capacity to trigger osteomyelitis.\textsuperscript{[24,25]} The bacteria adhere directly to the cartilage matrix and they form obstructive emboli in the metaphyseal vasculature causes local ischemia and necrosis.\textsuperscript{[24-26]} In our patient uncontrolled biliary system infection may possibly lead to osteonecrosis and osteomyelitis as a result of hematogenous dissemination of bacteria.

Here, we reported a patient with multifocal and exceptional location of osteonecrosis and osteomyelitis. Although ON is well known complication of after transplantation and steroid therapy, it generally located at femur head. As in our case; ON is rarely place on diaphyseal region of long bone with multifocal location, this

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2}
\caption{(a) Whole body leukocyte scintigraphy: compared to the symmetric side increased osteoblastic activity on the left knee, (b) Three-phase bone scintigraphy, perfusion phase: increased soft tissue perfusion and activity at left knee (c) Three-phase bone scintigraphy, blood pool-phase: increased osteoblastic activity at left knee (d) Three phase bone scan late-phase: increased activity at left knee and left ankle.}
\end{figure}
situation may be associated with the presence of uncontrolled infection.

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**REFERENCES**


