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CASE REPORT

Non-Hodgkin lymphoma as primary bone tumor in a patient with B hepatic viral infection - case report

Răzvan Ene* **, Zsombor Pánti* **, Marian Pleniceanu*, Mihai Nica* **, Mihnea Popa* **, Monica Cîrstoiu ***, Cătălin Cîrstoiu* ****
*Orthopedics Department, Emergency University Hospital Bucharest, Romania
**"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
***Obstetrics and Gynecology Department, Emergency University Hospital Bucharest, Romania
Correspondence to: Pánti Zsombor, MD, PhD,
Orthopedics Department, Emergency University Hospital Bucharest, Romania
169 Independenței Street, Code 050098, Bucharest, Romania,
Mobile Phone: +40740 082 338, E-mail: panti.zsombor@gmail.com

Abstract
Diffuse large B cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphomas, which has shown an increasing incidence in the past decades. 7% of primary bone tumors consist of non-Hodgkin lymphomas. The etiology of this type of lymphoma is still unclear. Our aim was to study the latest research papers; to highlight the importance of cooperation between different medical specialty departments, in rare cases like NHL as PBT with associated HBV infection.
Case report: We present the case of a 39-year-old male patient, who presented to the orthopedic department of the University Emergency Hospital of Bucharest, with moderate pain, swelling, and a palpable mass of the right lower limb.
Management and Outcome: The patient underwent several investigations, whose result was DLBCL and an associated HBV infection. Due to the aggressive form of DLBCL, chemotherapeutical treatment has to be initiated as soon as possible to prevent further growth of the tumor. An antiviral therapy had to be initiated to prevent the hepatic failure, which could appear after chemotherapy and in the acute phase of viral infection.
Discussion: Our case raised the question regarding what kind of relationship could be identified between the HBV infection and NHL, and how this condition influenced the outcome of the treatment.
Keywords: lymphoma, pathogenesis, prognosis

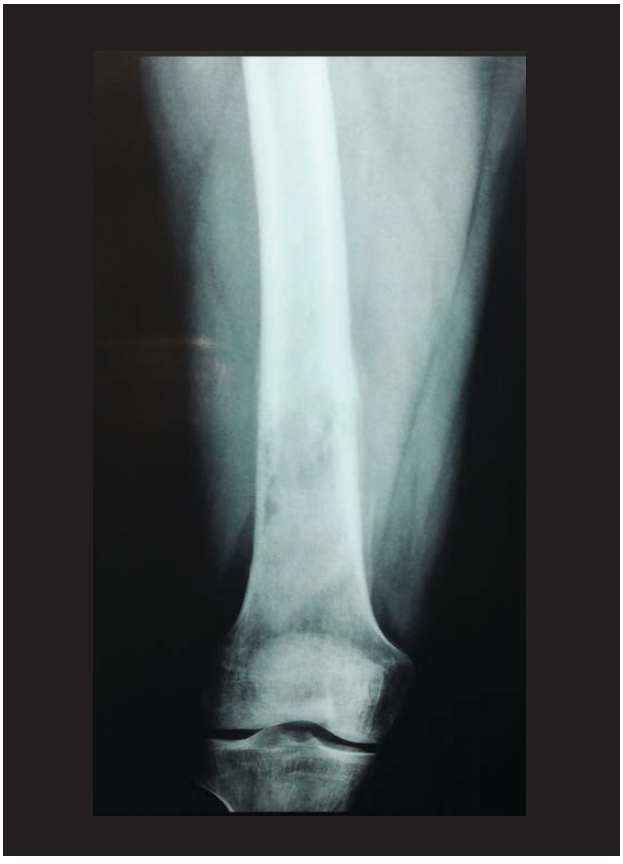
Introduction

Malignant proliferation of the lymphoid tissue is the most commonly occurring disorder in hematology [1]. The clinically, pathologically and genetically appearance of this transformation of cells is very diverse. There are two major, worldwide accepted, classes: Hodgkin (HL) and non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma contains several subtypes of which, the most common is the diffuse large B cell lymphoma (DLBCL). DLBCL is an aggressive, fast growing type of lymphoid cancer, with an increasing incidence in the past decades [2]. Because of the heterogeneity, clinical behavior and

response to therapy, the long-term outcome of the disease is very variable [3,4]. Due to variable clinical appearance of DLBCL, the patients often present to different specialty departments with different symptoms. 7% of primary bone tumors (PBT) consists of non-Hodgkin lymphomas, the clinical appearance usually consisting of localized slightly bone pain, and palpable mass [5,6]. The evaluation of patients with primary bone tumor is multi-disciplinary, which includes the radiologist, orthopedic surgeon, pathologist, oncologist, and hematologist. The etiology of non-Hodgkin lymphoma is still unclear; several studies underline the exposure of chemical, ultraviolet factors, the long-term use of immunosuppressive drugs, congenital immune deficiency, autoimmune diseases, and infections with Epstein Barr virus (EBV) and Human Immune virus (HIV). Early diagnosis and staging of DLBCL is crucial for the effective outcome of therapy [7,8]. Our aim was to study the latest research papers, to highlight the importance of cooperation between different medical specialty departments, in rare cases like NHL as PBT with associated HBV infection.

Case report

In the beginning of January 2013, a 39-year-old male patient presented at the orthopedic department of the University Emergency Hospital of Bucharest, with moderate pain and functional impotency of the right lower limb. According to the patient's mentions, the symptoms appeared 5 months earlier, in September 2013, when a slight pain appeared in the right lower limb. The pain was not specific, usually non-steroid anti-inflammatory drugs (NSAID) relieved it. After 2 weeks, the symptoms reappeared with irradiation to the back, and became more disturbing. During the physical clinical examination, a palpable mass was evidenced on the anterior right distal part of the thigh. The approximate dimension of the tumor was 10/ 7 cm. Other remarkable findings of physical examination like regional adenopathies, hepato- or splenomegaly were not identified. During the examination of biological markers, the erythrocyte sedimentation rate ESR was high (37 mm/ h; N:5-10 mm/ h), as well as fibrinogen (603.9 mg/ dL; N: 200-400 mg/ dL). The qualitative virology test was positive for the HBsAg and negative for HCV and HIV. After the underlying HBV infection, the patient was interrogated again, the focus being on the viral infections. The patient mentioned the following infections in his anamnesis: HHV1, HHV2, VZV in childhood, he denied any blood transfusions, unprotected sexual contacts in the past, however a tattoo was made in April 2013. In the beginning of January 2014, an MRI was made for the investigation of the lower back pain, because a herniated spinal disc was suspected. The result of the MRI was negative. CT, MRI scans, and X-ray were also made for the investigation of the leg pain, which showed a space occupying process in the distal part of the anterior femoral region, without any regional adenopathies (Fig. 1,2).



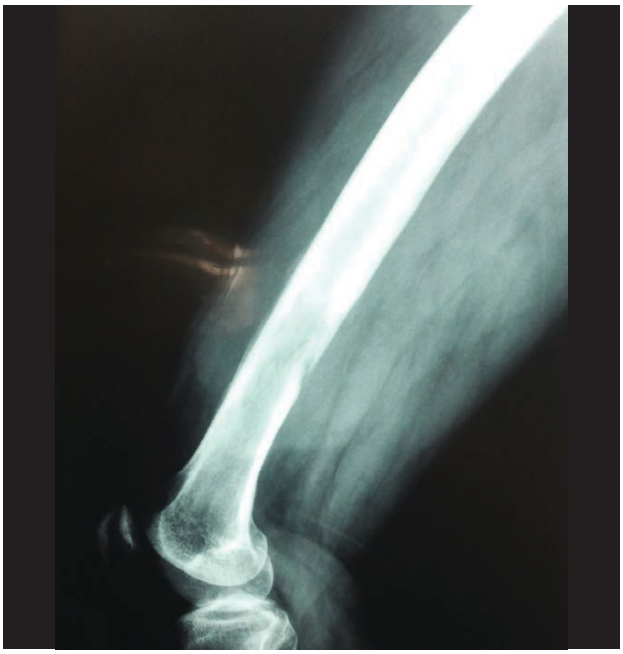


Fig. 1 X-ray of the right distal femur, anterior and lateral view, showing osteolitic lesions, with slight periostal reaction

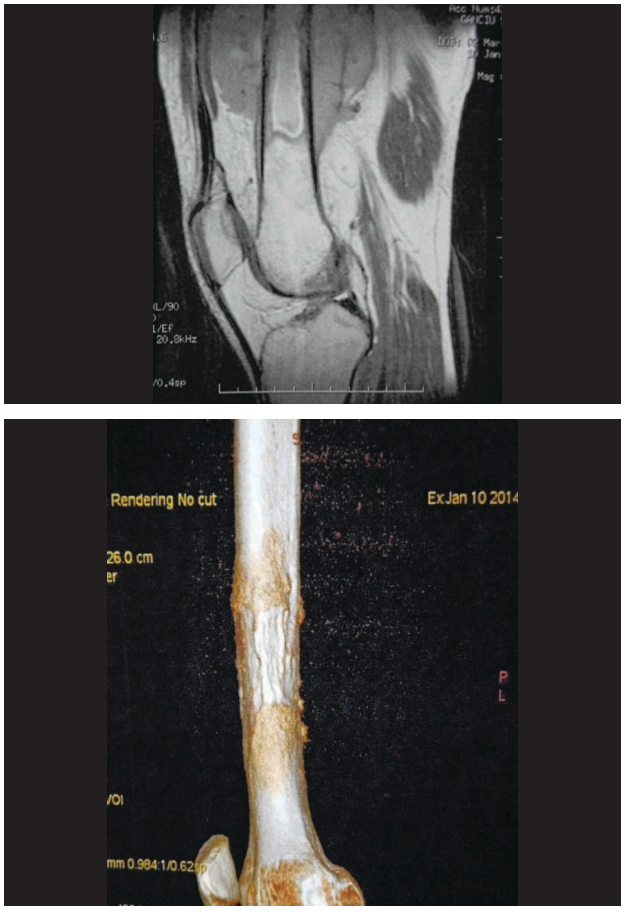


Fig. 2 The MRI scan describes the space occupying process on the distal third of the femur (on the left). 3-D reconsturction of MRI showes cortical lesions, and periostal reaction on the level of the tumor (on the right)

For further investigation, a three-phase bone scintigraphy with technetium-99m-MDP was executed on the tumor region with the following findings: increased vascularization and metabolism of the tumoral tissue region, hyperfixation of the distal femur (Fig. 3).

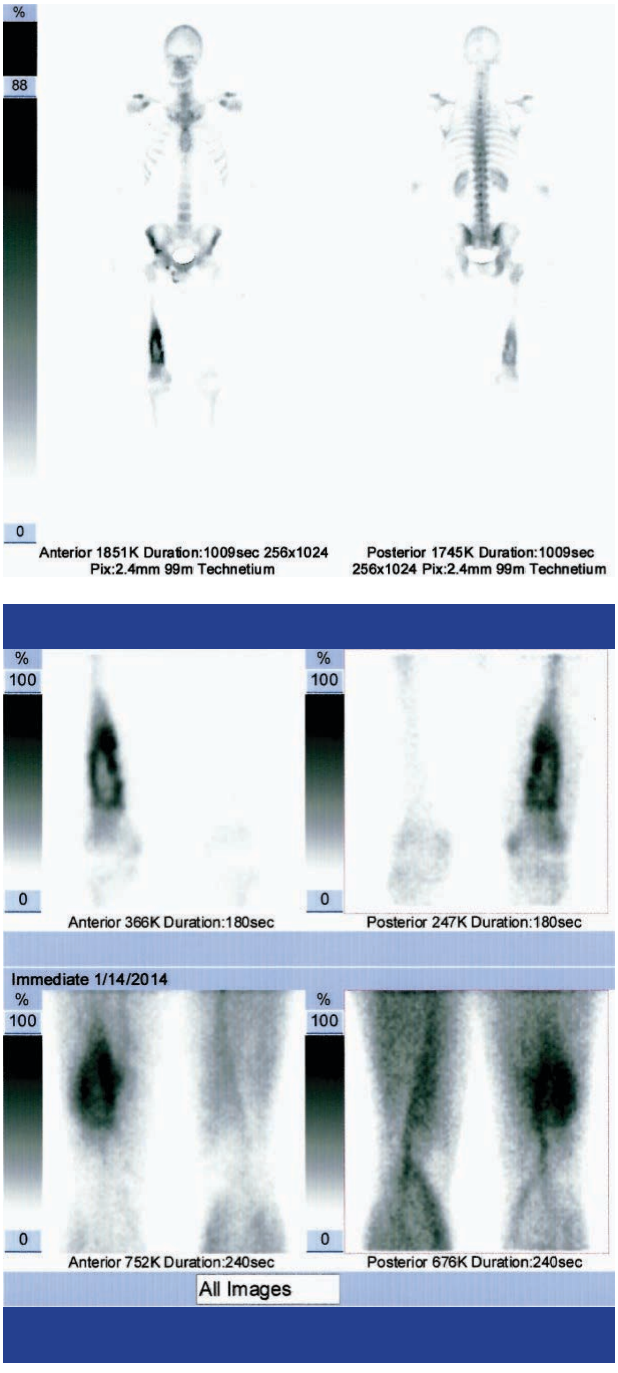


Fig. 3 Bone Scintigraphy, showing an increased sign of right distal femoral region in metabolic phase

The SPECT/ CT describes an unregulated border of the tumor tissue (Fig. 4).

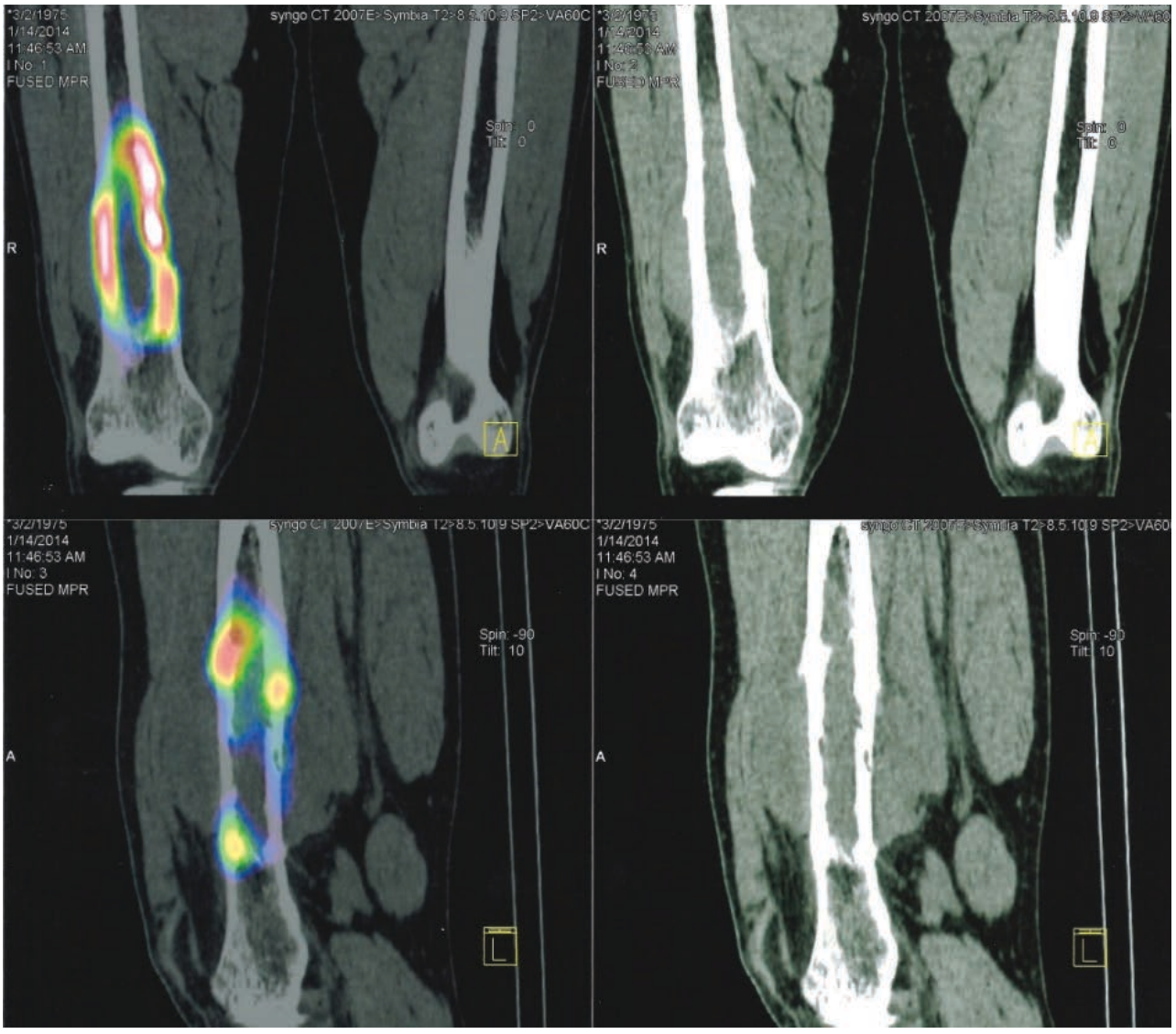


Fig. 4 SPECT/ CT

Furthermore, a thoracic and lower limb CT was made. The thoracic CT examination described the sequels of Sheuermann's disease, without any anomalies of the mediastinum, while the CT of the right distal femoral region showed osteolysis of the distal endosteum and popliteal microadenopaties. Angiography showed increased vascularization with tumor aspect for the suspected tissue area. After the incision biopsy, the histological result was non-Hodgkin lymphoma. Immunohistochemistry (IHC) confirmed the following B cell type with the following findings: CD45, CD20, CD30 (lower positivity) and high (80-85%) Ki67 proliferation.

After the diagnosis, other markers like Alfa Feto Protein (AFP) with an increased value (1.95 ng/ ml), and HBsAg with 728.39 s/ c (normal values 0-1 s/ c) were investigated.

Discussion

Our case raised the following question: what kind of relationship could be identified between the HBV infection and NHL, and how that condition influenced the outcome of the treatment. A recent study by Samir Dalia et al. shows that there is a 2.24 times increase in the odds of developing NHL in patients with HBV infection [9]. The mechanism between this relation is still unclear. The most likely

hypothesis is that the HBV-specific nucleic acid appears in peripheral blood mononuclear cells and in hematopoietic tumor cells, which stimulates the B cells. This condition may lead to the appearance of NHL, due to chronic stimulation of B cells. It is well known that the presence of HBV-encoded x protein inhibits the p53 tumor suppressor protein in liver cells; a similar mechanism could lead to B cell malignant proliferation [9,10]. According to the patient's anamnesis, the symptoms of the tumor appeared after the possible beginning of the infection with HBV (April 2013). There was a 6 months interval between the possible beginning of HBV infection and the appearance of the symptoms of the lower limb. The aforementioned possible mechanisms could be the explanation of the appearance of NHL in the case of our patient. Another relation between the chronic HBV infection and NHL was that the treatment of NHL with rituximab might reactivate the HBV infection. Rituximab is an antibody that targets the CD20 antigen, which is present in the surface of malign transformed B cells [11,12]. In our case, rituximab, as standard chemotherapy, played an important role in the therapy of DLBCL, but due the high risk of HBV reactivation, this treatment has to be avoided. Authors recommended a prophylactic antiviral therapy with nucleoside analog like lamivudine before the administration of rituximab. Several theories have been published for the explanation of the reactivation of hepatitis. First, rituximab may lead to direct hepatic toxicity; secondly, there is a repress of T cells; thirdly, a rebound immune mechanism may affect the viral antibody presenting hepatic cells [11-13]. Due to the high aggressive type of lymphoma (Ki67 80-85%), the chemotherapeutical treatment in our case had to be initiated as soon as possible to prevent the further growth of the tumor, and the appearance of metastases. There was also a need to initiate an antiviral therapy, which was recommended by several authors. Newer studies showed that this therapy should be continued after the last cycle of chemotherapy for a period of 6 months. Extended use of lamivudine may lead to resistance, therefore new antivirals like adefovir or tenofovir should be examined for their lower resistance rate and for a longer antiviral therapy [13-15]. The findings of a recent study by Changhong Liu et al. show that the treatment of chronic hepatitis with entecavir is as safe as lamivudine, however, entecavir is able to inhibit HBV replication, decreases the HBV DNA faster and efficiently, in our case being crucial to begin chemotherapy as soon as possible [16].

Conclusions

DLBCL is an aggressive fast growing tumor (...cm to 7/ 10cm in a period of 5 months), younger patients may be affected as well. The presence of HBV infection complicated the chemotherapeutical treatment with rituximab in our patient. An antiviral therapy is indispensable, and has to be initiated as soon as possible to prevent the evolution of the tumor.

The relationship of the HBV infection on B cell proliferation is still unclear; however, some studies underline the HBV infection like an etiology factor in the appearance of DLBCL. This entity opens new experimental possibilities.

Due to the unspecific clinical appearance of this disease, a multidisciplinary cooperation is needed for the fast diagnosis and for the fast staging. The diagnosis of DLBCL requires further investigations in every patient for the detection of HBV infection.

The untreated HBV infection and the application of chemotherapy in DLBCL may lead to a liver failure, which worsens the prognosis for hepatitis and for DLBCL as well.

References

1. Cheson B et al. Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma. New England Journal of Medicine. 2008; 359:613-626.
2. Menon MP, Pittaluga S, Jaffe ES. The Histological and Biological Spectrum of Diffuse Large B-cell Lymphoma

in the WHO Classification. Cancer J. 2012 September; 18(5):411–420.
3. Kwak JY. Treatment of Diffuse Large B Cell Lymphoma. Korean J Intern Med. 2012; 27:369-377.
4. Ruzek KA, Wenger DE. The multiple faces of lymphoma of the musculoskeletal system. Skeletal Radiol. 2004; 33:1–8.
5. Caporale MF et al. Non-Hodgkin's lymphoma: unexpected cause of shoulder pain. A systematic review of the literature. Muscles, Ligaments, and Tendons Journal. 2013; 3(3):236-239.
6. Baar J, Burkes RL, Gospodarowicz M. Primary non-Hodgkin's lymphoma of bone. Semin Oncol. 1999 Jun; 26(3):270-275.
7. Engels EA. Infectious Agents as Causes of Non-Hodgkin Lymphoma. Cancer Epidemiol Biomarkers Prev. 2007; 16:401-404.
8. Zhang Y et al. Ultraviolet radiation exposure and risk of non-Hodgkin's lymphoma. Am J Epidemiol. 2007 Jun 1; 165(11):1255-1264.
9. Samir D, Chavez J, Castillo JJ, Sokol L. Hepatitis B infection increases the risk of non-Hodgkin lymphoma: A meta-analysis of observational studies. Leukemia Research 37. 2013; 1107–1115.
10. Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. Blood. 2011; 117(6):1792-1798.
11. Yang JD, Girotra M, Vaid A, Duarte-Rojo A. Hepatitis B reactivation in patient with non-Hodgkin's lymphoma receiving rituximab-based chemotherapy: need for education and attention. J Ark Med Soc. 2013 Nov; 110(6):110-2.
12. Plosker GL, Figgitt DP. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. Drugs. 2003; 63(8):803-43.
13. Dong HJ, Ni LN, Sheng GF, Song HL, Xu JZ, Ling Y. Risk of hepatitis B virus (HBV) reactivation in non-Hodgkin lymphoma patients receiving rituximab-chemotherapy: a meta-analysis. J Clin Virol. 2013 Jul; 57(3):209-14.
14. Lee IC, Huang YH, Chu CJ, Lee PC, Lin HC, Lee SD. Hepatitis B virus reactivation after 23 months of rituximab-based chemotherapy in an HBsAg negative, anti-HBs-positive patient with follicular lymphoma. J Chin Med Assoc. 2010; 73:156–60.
15. Davis J. Preventing hepatitis B virus reactivation following immunosuppressive therapy. Intern Med J. 2008; 38:617, author reply 17-18.
16. Changhong Liu et al. Entecavir and lamivudine therapy for severe acute chronic hepatitis B. Experimental and Therapeutic Medicine. 2013; 5:545-548.