

Hodgkin's lymphoma coexisting with liver failure secondary to acute on chronic hepatitis B

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Received: August 15, 2012 Revised: October 4, 2012

Accepted: November 11, 2012

Published online: April 16, 2013

Abstract

Acute on chronic liver failure (ACLF) is rarely the initial manifestation of a malignant process or precipitated by the initiation of anti-viral treatment with a nucleoside or nucleotide agent. We report an unusual case of ACLF temporally associated with initiation of Entecavir for treatment of chronic hepatitis B. Early Hodgkin's lymphoma (HL) was unmasked with initiation of the anti-viral treatment which may have exacerbated ACLF. To the best of our knowledge, this has not been described in the literature. In reviewing our patients clinical course and liver autopsy, he developed a severe acute exacerbation of his chronic hepatitis B virus coinciding with the institution of antiviral therapy and the underlying HL perhaps modulating the overall degree of hepatic injury.

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Key words: Entecavir; Hepatic flare; Fulminant hepatic failure; Chronic hepatitis; Acute liver failure; Hodgkin's lymphoma

Palta R, McClune A, Esrason K. Hodgkin's lymphoma coexisting with liver failure secondary to acute on chronic hepatitis B. *World J Clin Cases* 2013; 1(1): 37-40 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v1/i1/37.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v1.i1.37>

INTRODUCTION

Chronic hepatitis B virus (HBV) is a worldwide clinical problem. The natural progression of HBV is determined by the hosts' immune system and viral replication. HBV flares can be elicited by withdrawal of an immunosuppressive therapy, exposure to another hepatitis or malignancy or can occur spontaneously due to an intensification of the hosts' immunologic response to the HBV virus^[1]. The pathogenesis of hepatic flares are suspected to be due to changes in immunologic control of viral replication which precipitate an increase in T-cell reactivity to the hepatitis virus. Antiviral treatment viral restores T-cell responsiveness allowing for suppression of viral replication and may precipitate hepatic flares early in treatment. Withdrawal of anti-viral therapy can allow for development of viral mutations^[1]. Entecavir and Tenofovir are potent HBV inhibitors with a high barrier to resistance and have been noted to achieve virological response in patients with severe acute exacerbations of chronic HBV^[2].

Hepatic involvement by Hodgkin's lymphoma (HL) typically manifest with large tumor infiltration leading to hepatocyte destruction, duct necrosis and subsequent liver failure. The diagnosis of Hodgkin's disease requires presence of mononuclear Reed-Sternberg cells. Hepatic involvement of HL usually indicates Stage IV disease and rarely presents as the initial manifestation of acute liver failure (ALF)^[3].

CASE REPORT

A 57-year-old Asian physician with a history of verti-

cally transmitted inactive chronic hepatitis B diagnosed in 1985 presented for routine health examination in August 2010 and liver tests were noted to be abnormal: aspartate aminotransferase (AST) 77 IU/L and alanine aminotransferase (ALT) 79 IU/L.

Two months later, AST and ALT had risen to 83 IU/L and 102 IU/L, respectively. HBV DNA level was > 110 000 000 IU/mL. Hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen negative and hepatitis B e antibody positive. Hepatitis B core immunoglobulin (IgM) negative, hepatitis B core IgG positive. International normalized ratio (INR) was normal. Abdominal ultrasound was unremarkable. Repeat laboratory examination demonstrated AST 165 IU/L, ALT 230 IU/L and total bilirubin (T.bili) 1.1 mg/dL. Entecavir 0.5 mg daily was initiated. Follow-up labs 1 mo later demonstrated AST 917 IU/L and ALT 1225 IU/L, INR 1.6, T.bili 2.4 mg/dL and a lower HBV DNA level of 3 198 626 IU/mL.

He presented 6 wk later with complaints of abdominal pain and jaundice. On physical examination, his heart rate was 110-125 beats per minute with normal blood pressure. He had no stigmata of chronic liver. Mild abdominal tenderness noted with minimal ascites and no palpable masses. Lymphadenopathy was not appreciated. Edema and asterixis were absent.

AST and ALT were 1169 IU/L and 1472 IU/L, respectively, INR 2.2 and T.bili 5.7 mg/dL. HBV DNA was 322 029 IU/mL. Serological tests for hepatitis A, hepatitis C, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, Wilson's disease, autoimmune liver disease, thyroid disease, α 1 anti-trypsin deficiency and hemochromatosis were all within normal limits. Serum and urine toxicology screens were negative. Hepatitis E IgG and IgM were negative.

Abdominal ultrasound suggested early cirrhosis with splenomegaly and a patent portal vein. Non-contrast computed tomography (CT) scan of abdomen confirmed a mildly nodular liver surface compatible with early cirrhosis, a mildly enlarged spleen and small to moderate ascites. No masses, gallbladder stones or biliary dilatation was seen. Asymmetrical right external iliac adenopathy and right inguinal adenopathy were noted on CT scan. Chest X-ray (CXR) was normal. Transthoracic echocardiogram demonstrated an ejection fraction of 65%-70% with right ventricular systolic pressure measured at 24-29 mmHg.

Six weeks after initiation, Entecavir was held in the emergency department given a concern for a potential side effect of the medication. The patient was started on N-acetylcysteine intravenously and on vitamin K. Only a minimal amount of ascites was visualized on ultrasound, therefore a paracentesis was not performed. Empiric piperacillin and tazobactam was initiated for presumed spontaneous bacterial peritonitis (SBP).

The aminotransferases improved but the bilirubin and INR continued to rise. Blood and urine cultures were negative. He was transferred to University of California Los Angeles (UCLA) for orthotopic liver transplant evaluation.

To prevent worsening hepatic failure and to prevent the emergence of a drug-resistant mutation secondary to abrupt discontinuation of Entecavir therapy, he was started on Tenofovir 300 mg daily at the UCLA Medical Center. Repeat HBV DNA level of 5 IU/mL. Paracentesis was positive for SBP and Ceftriaxone was initiated. The ascites culture and cytology were negative. Repeat CT scan of the abdomen/pelvis at UCLA confirmed cirrhosis. No hepatic masses or biliary dilatation were noted. Ascites, splenomegaly and bilateral small pleural effusions were present.

His mental and respiratory status deteriorated, necessitating intubation and mechanical ventilation. He developed fevers and CXR demonstrated increasing pulmonary vascular congestion. Antibiotic coverage was broadened to intravenously vancomycin and piperacillin/tazobactam.

Three days after intubation, sedatives were held in order to assess his mental status. Non-contrast head CT scan did not demonstrate any abnormalities. He remained unresponsive with a spontaneous gag and cough reflex. Non-contrast CT scan of the chest demonstrated diffuse ground glass opacities bilaterally with consolidation throughout the lungs consistent with Acute Respiratory Distress Syndrome (ARDS). Prominent mediastinal lymph nodes measuring up to 10 mm were also visualized but attributed to be most likely reactive changes to ARDS. Non-contrast brain CT demonstrated interval development of malignant cerebral edema.

Patient's overall clinical status deteriorated further requiring multiple vasopressor support and continuous renal replacement therapy. The patient's family withdrew care. Cause of death was acute on chronic liver failure (ACLF) complicated by multisystem organ failure and acute brain stem herniation.

Autopsy was limited to the liver. The liver was small with micro-nodular cirrhosis. Histology demonstrated diffuse hepatocyte necrosis with florid reactive bile duct proliferation and acute collapse of hepatic parenchyma. Immunohistochemistry was negative for hepatitis B surface and core antigens. Histological examination of a single 0.7 cm subcapsular nodule on the superior surface of the liver revealed mixed inflammatory infiltrative cells composed of small mature lymphocytes and scattered atypical multinucleated cells consistent with Reed-Sternberg cells. Immunohistochemical studies were positive for CD20, CD30, fascin, Epstein-Barr virus-encoded small RNA, consistent with HL.

DISCUSSION

Chronic HBV affects more than 350 million people worldwide. Complications of HBV include development of hepatocellular carcinoma or decompensated cirrhosis. In rare instances, chronic HBV patients can develop spontaneous severe acute exacerbations of the disease that result in hepatic failure and death^[2]. Acute flares of HBV are caused by withdrawal of immunosuppressive

medications, antiviral therapy and HBV genotypic variations. Occasionally, acute exacerbations are spontaneous^[1].

We report a case of fatal ACLF associated with undiagnosed HL and initiation of anti-viral treatment.

Review of the literature did not reveal any reports implicating HL as a catalyst for acute on chronic hepatic failure. However, HL has been associated with fulminant hepatic failure (FHF)^[3,4].

HL can lead to liver dysfunction through several mechanisms^[3-6] which include (1) tumor infiltration of hepatic vasculature, bile ducts and/or hepatic parenchyma; (2) vanishing bile duct syndrome from cytokine release; (3) as a paraneoplastic phenomenon; and by (4) withdrawal of chemotherapeutic agents in HBV positive individuals. In cases where HL is implicated with FHF, patients typically have been treated with chemotherapy and ALF is secondary to reactivation of HBV^[7]. To the best of our knowledge, HL has never been implicated as an eliciting factor to an acute exacerbation of chronic HBV.

HL most commonly presents as painless lymphadenopathy with hepatic manifestations usually occurring in advanced stage disease. Liver test abnormalities or ALF is rarely seen as the initial manifestation of HL and often only detected post-mortem^[8-12].

FHF can present in 5%-8% of patients with HL^[8,13,14], although, in reported cases, the patients usually had established malignancies^[9-12]. Most reports of FHF in HL implicate diffuse hepatic infiltration as the etiology^[13]. Rarely, is FHF an initial presentation of non-metastatic HL^[8,14-16].

An 18-year retrospective review of ALF patients by Rowbotham *et al*^[3] reported that 18 out of 4020 patients (0.44%) were found to have ALF secondary to malignant infiltration. HL was seen in only 0.07% (3 of 4020) cases. In the three cases where HL was implicated as the cause of ALF, two had previously been diagnosed with HL and had a history of chemotherapy.

Recommended treatment for patients with an acute flare of HBV is early initiation of oral nucleoside analogs to suppress HBV DNA viral replication^[1,2]. Early suppression may decrease the number of hepatocytes expressing HBV antigens thereby reducing the target burden for the immune response, allowing the flare to settle. Nucleoside analogs lack a direct immunologic effect and have a rapid effect on viral replication as compared to Interferon therapy^[1]. Anti-viral therapy has not impacted short-term survival but has improved long-term outcomes by preventing future exacerbations and ongoing liver injury^[1,2].

Entecavir is a potent nucleoside analogue with low rates of antiviral resistance (< 1% at 2 years in treatment-naïve subjects) and has been widely adopted for routine use in patients with HBV infection^[13].

Several studies have documented the benefits of entecavir therapy in ACLF in HBV. Shu *et al*^[17] reported that entecavir improved overall survival in 84 HBeAg negative patients. Jochum *et al*^[18] reported that entecavir improved outcomes in 6 patients with ACLF. In 5 out of 6 of these

cases, seroconversion to anti-HBsAg was achieved with normal or trace amounts of HBV DNA within 3 mo. Chen *et al*^[19] reported improved survival among 352 patients with ACLF after initiation of lamivudine, entecavir or telbivudine. Wong *et al*^[20] suggested long-term survival benefit among ACLF if anti-viral therapy (specifically lamivudine) was initiated early (bilirubin less than 20 mg/dL).

In 2011, Wong *et al*^[20] reviewed short and long term mortality in a small cohort of patients with ACLF who were treated with entecavir compared to lamivudine. Entecavir use was independently associated with increased short-term mortality but had a higher virological and biochemical response at week 48. The cause of increase in short-term mortality is not understood.

In conclusion, ACLF is an uncommon but well recognized complication of hepatitis B. In many instances, the eliciting trigger is identifiable and treatment with anti-viral therapy is beneficial for long-term mortality. Patients HL typically manifest their disease with systemic symptoms or diffuse hepatic infiltration and rarely present with FHF^[6,11]. HL without prior treatment with chemotherapy has not been implicated as a trigger for an acute exacerbation of HBV.

This report is a case of fatal acute on chronic hepatic failure that may have been accelerated by undiagnosed HL and/or initiation of anti-viral treatment. In reviewing our patients clinical course and liver autopsy, he developed a severe acute exacerbation of his chronic HBV coinciding with the institution of antiviral therapy and the underlying HL perhaps modulating the overall degree of hepatic injury.

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P- Reviewers Jin B, Said NZA, Wirth S, Sookoian S
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