CASE REPORT

Fulminant hepatitis following chemotherapy treatment for breast cancer

Ali Hakim Shoushtari,¹ Robert A Shaw²

¹Clinical and Translational Science Institute, Pittsburgh, Pennsylvania, USA
²East Carolina University, Greenville, North Carolina, USA

Correspondence to
 Dr Robert A Shaw,
 shawr@ecu.edu

SUMMARY

A woman in her early 50s was admitted to the intensive care unit with nausea, altered mental status and hepatic failure. She had a history of asymptomatic chronic hepatitis B and recently received chemotherapy for breast cancer. A diagnosis of hepatitis B reactivation (HBR) was made, but unfortunately she died of liver failure. Controversies around testing for hepatitis B prior to giving immunosuppressive treatments and the use of prophylactic antiviral therapy to prevent HBR are discussed.

BACKGROUND

There are currently 800 000–1.4 million residents of the USA chronically infected with the hepatitis B virus (HBV). Worldwide, the prevalence of HBV infection varies from 10% to 25% in endemic areas to less than 1% in many western countries.^{1–3} HBV infection can be acute or chronic. Chronic HBV-infected patients are often asymptomatic; however, a variety of serological markers are positive. Figure 1 illustrates the course of serological changes in acute HBV infection with progression to chronic HBV infection.

Some of the patients with chronic HBV infection develop malignancy (unrelated to chronic hepatitis) and require chemotherapy. The immune suppression from chemotherapy can then lead to reactivation of the hepatitis. Clinical manifestation of HBR can vary from a self-limiting asymptomatic hepatitis to severe, fulminant hepatic failure.^{2 5–10} In the past, it has been controversial whether all patients who are to receive chemotherapy should be tested for hepatitis B. Additionally, in patients who have serological markers positive for chronic hepatitis B, it is not certain whether chemotherapy treatment should be delayed in order for them to receive antiviral therapy first.^{5 11} We present an unfortunate patient who developed HBR following chemotherapy for breast cancer.

CASE PRESENTATION

A woman in her early 50s was admitted to the intensive care unit because of intractable nausea, altered mental status, dehydration and jaundice. Three years before this admission, she was diagnosed with asymptomatic hepatitis B during a routine physical. At that time, she denied risk factors for viral hepatitis such as tattoos, intravenous or intranasal drug use, prison time or blood transfusions prior to 1992. She denied multiple sexual partners and ingested one alcoholic beverage every 2–3 weeks. Her brother and father had previously been diagnosed with hepatitis B. The diagnosis of hepatitis B

in our patient was made by the following tests: hepatitis B envelope (HBe) antigen was positive, HBe antibody was negative and hepatitis B viral load was 168 million copies/ml. Her liver enzymes were elevated: alkaline phosphatase 129 IU/l (normal 41–120 IU/l), aspartate transaminase (AST) 57 IU/l (normal 10–31 IU/l) and alanine transaminase (ALT) 1308 IU/l (normal 10–41 IU/l). Her gastroenterologist wanted to treat her with adefovir, but there is no record that she followed up with him or took the medicine. Five months before this admission, she had a partial mastectomy for stage 3 node positive breast cancer. Four months before admission, she started the first of four cycles of chemotherapy with Taxotere, epirubicin and cyclophosphamide. Prior to the chemotherapy, she had no symptoms of liver disease, and liver enzymes were normal except for slight elevation in the alkaline phosphatase of 159 IU/l (normal 20–140 IU/l). Hepatitis B markers were not measured immediately before giving the chemotherapy. She was not given any prophylactic antiviral therapy prior to receiving chemotherapy.

One month after finishing chemotherapy, she developed fatigue, weakness, nausea and a striking elevation of transaminases with AST 1414 and ALT 1308 IU/l. HBV DNA was 955 million copies/ml. Immunoglobulin (IgM) antihepatitis B core antigen (HBc) was positive. Antibodies to hepatitis A and C antigens were negative. HBe antibody was negative and HBe antigen was positive. Hepatitis B surface (HBs) antibody was borderline positive and HBs antigen was positive. The gastroenterologist diagnosed HBR based on the patient's history of no exposure to alcohol, absence of other immunological diseases and the laboratory tests. He initiated treatment with entecavir 1 mg per oral each day. This resulted in an immediate drop in her hepatitis B viral load 4 days later to 21 million copies/ml. Her symptoms progressed, however, and she was admitted to the ICU 2 weeks later.

During the ICU admission, she developed fulminant hepatic failure due to HBR. She continued on entecavir and received steroids. She had progressive deterioration with coagulopathy, retroperitoneal bleeding, hepato-renal syndrome and coma. Due to the poor prognosis, her family requested withdrawal of aggressive treatments, and she died.

INVESTIGATIONS

In addition to the tests mentioned above, other test results after admission to the ICU included: prothrombin time 43.6 s (normal 9.7–11 s), total bilirubin 19.8 mg/dl (normal 0.3–1.2 mg/dl), alkaline

To cite: Shoushtari AH, Shaw RA. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007017

Figure 1 Course of serological changes in acute and chronic hepatitis B virus (HBV) infection. Scheme adapted from Weinbaum *et al.*⁴

phosphatase 115 IU/l (normal 41–120 IU/l), AST 372 IU/l (normal 10–31 IU/l), ALT 220 IU/l (normal 10–41 IU/l) and serum albumin 2.6 g/dl (normal 3.4–4.9 g/dl). She developed severe anaemia, and an abdominal CT scan showed left-sided retroperitoneal bleeding, which was most likely due to the coagulopathy. No sign of cancer was seen in the liver. Subsequent liver function tests remained abnormal. A brain CT scan was performed because of coma and was negative. No further testing was performed at the family's request.

DIFFERENTIAL DIAGNOSIS

HBR due to chemotherapy and chemotherapy-induced liver injury were considered when the patient developed fatigue, nausea and elevation of transaminases. The gastroenterologist made the diagnosis of HBR after blood tests demonstrated large hepatitis B viral load and positive IgM anti-HBc antibody. Alcoholic hepatitis, other viral hepatitis and cancer were ruled out by the patient's history, serological tests and imaging studies.

TREATMENT

The patient was treated with entecavir, intravenous steroids and hydration. She also received blood transfusion, midodrine, octreotide, continuous renal replacement therapy and antibiotics.

OUTCOME AND FOLLOW-UP

The patient died of hepatic failure with coagulopathy, retroperitoneal haemorrhage, hepatic coma and hepatorenal syndrome. The family withdrew care.

DISCUSSION

HBR has only recently achieved attention in the oncology world. It is now recognised as an important consideration in treating patients with chemotherapy and other immunosuppressive treatments. HBR is a known phenomenon which was first described in the treatment of haematological malignancies.^{10–12–13} The proposed mechanism for this phenomenon is the formation of a covalently closed circular DNA in infected hepatocytes' nuclei within 24 h of HBV infection, which leads to HBV persistence.^{2–5–7} Immunosuppression caused by the use of chemotherapy allows the increase of HBV replication

and, hence, expression of surface antigens on hepatocytes. Furthermore, immune system restoration after or between cycles of chemotherapy causes T cell (specifically cytotoxic CD8+) mediated destruction of infected hepatocytes. Clinical manifestations of HBR can vary from a self-limiting asymptomatic hepatitis to severe, fulminant hepatic failure.^{2–5–10}

The current diagnostic criteria for HBR is the occurrence of hepatitis during or immediately after chemotherapy (commonly 4–36 weeks).⁵ Hepatitis is defined by a greater than twofold increase of ALT or an increase of >100 IU/l ALT associated with an increased HBV DNA level of >10⁹ copies/ml or >10-fold increase from baseline.^{2–5–14–16} However, serial monitoring of ALT and HBV DNA often demonstrates that the HBV DNA surge precedes ALT rise by up to 3 weeks.⁵ Therefore, close monitoring of ALT and HBV DNA can provide an early diagnosis of HBR.

The risk of developing HBR is higher in breast cancer patients who receive chemotherapy (28–56%) than for other solid tumours (14–21%).¹⁵ Yeo *et al.*¹⁵ identified the following risk factors for HBR: detectable prechemotherapy HBV DNA load, the use of steroids, diagnosis of lymphoma or breast cancer and use of anthracyclines. The amount of immune suppression rather than cancer type is probably the most important factor. In patients with solid tumours, the prognosis of HBR is unclear. Spontaneous resolution of viral reactivation is common.⁵ The reported mortality of patients with HBR treated with lamivudine has been reported up to 20%.⁵

In 2009, the US Centers for Disease Control (CDC) issued 'Recommendations for identification and public health management of persons with chronic hepatitis B virus infection'.¹⁷ It states, "Persons receiving cytotoxic or immunosuppressive therapy (eg, chemotherapy for malignant diseases, immunosuppression related to organ transplantation and immunosuppression for rheumatologic and gastroenterological disorders) should be tested for serologic markers of HBV infection (including HBsAg, anti-HBc and anti-HBs). Prophylactic antiviral therapy can prevent reactivation in HBsAg-positive patients."¹⁷ The American Society of Clinical Oncology (ASCO) subsequently published a provisional clinical opinion (PCO) directed towards oncologists practicing in the USA.^{18–19} The PCO stated, "However, the net benefits and harms of general population screening for chronic HBV cannot be estimated, because there is insufficient evidence of the precise risks of HBV reactivation across various malignancies and specific treatment regimens."¹⁹ They went on to state, "The PCO recommends that HBV screening follow clinical judgment based on the estimated risk of an individual being a carrier and the degree of planned immunosuppressive therapy (including hematopoietic cell transplantation and rituximab-containing regimens)."^{18–19} Additionally, an Australian article suggested that testing for all HBV serology markers in patients with solid tumours is not cost effective, and each physician individually should decide whether or not to screen for HBV.²⁰

We believe that the CDC recommendations for HBV infection serology screening before initiating chemotherapy are prudent. Patients who are HBV serology positive should make an informed decision regarding prophylactic treatment. In patients who will be severely immunosuppressed, the risk of HBR and fulminant hepatic failure should be discussed. Further data analysis of this complicated issue should be done to help determine which patients should be given prophylactic antiviral therapy prior to receiving chemotherapy.

Learning points

- ▶ Before treating patients with chemotherapy and other potent immunomodulators, prior hepatitis B status should be evaluated.
- ▶ Current diagnostic criteria for hepatitis B reactivation (HBR) include the occurrence of hepatitis during or immediately after chemotherapy (4–36 weeks) with increased hepatitis B virus (HBV) DNA level of $>10^9$ copies/ml or >10 -fold increase from baseline.
- ▶ HBR has variable prognosis, and severe cases can result in fulminant hepatic failure.
- ▶ Delaying chemotherapy in patients with chronic HBV infection in order to administer prophylactic antiviral therapy is controversial.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Lok AS, Lai CL, Wu PC, *et al.* Hepatitis B virus infection in Chinese families in Hong Kong. *Am J Epidemiol* 1987;126:492–9.
- 2 Lok AS, Liang RH, Chiu EK, *et al.* Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991;100:182–8.
- 3 Jilg W, Hottentrager B, Weinberger K, *et al.* Prevalence of markers of hepatitis B in the adult German population. *J Med Virol* 2001;63:96–102.
- 4 Weinbaum CM, Williams I, Mast EE, *et al.* Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008;57(RR-8):1–20.
- 5 Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006;43:209–20.
- 6 Targhetta C, Cabras MG, Mamusa AM, *et al.* Hepatitis B virus-related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo- or chemo-immune therapy. *Haematologica* 2008;93:951–2.
- 7 Westhoff TH, Jochimsen F, Schmittl A, *et al.* Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. *Blood* 2003;102:1930.
- 8 Liu CJ, Chen PJ, Lai MY, *et al.* A prospective study characterizing full-length hepatitis B virus genomes during acute exacerbation. *Gastroenterology* 2003;124:80–90.
- 9 Hoofnagle JH, Dusheiko GM, Schafer DF, *et al.* Reactivation of chronic hepatitis B virus infection by cancer chemotherapy. *Ann Intern Med* 1982;96:447–9.
- 10 Xunrong L, Yan AW, Liang R, *et al.* Hepatitis B virus (HBV) reactivation after cytotoxic or immunosuppressive therapy—pathogenesis and management. *Rev Med Virol* 2001;11:287–99.
- 11 Yeo W, Chan PK, Chan HL, *et al.* Hepatitis B virus reactivation during cytotoxic chemotherapy-enhanced viral replication precedes overt hepatitis. *J Med Virol* 2001;65:473–7.
- 12 Liang R, Lau GK, Kwong YL. Chemotherapy and bone marrow transplantation for cancer patients who are also chronic hepatitis B carriers: a review of the problem. *J Clin Oncol* 1999;17:394–8.
- 13 Galbraith RM, Eddleston AL, Williams R, *et al.* Fulminant hepatic failure in leukaemia and choriocarcinoma related to withdrawal of cytotoxic drug therapy. *Lancet* 1975;2:528–30.
- 14 Yeo W, Chan PK, Zhong S, *et al.* Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000;62:299–307.
- 15 Yeo W, Zee B, Zhong S, *et al.* Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 2004;90:1306–11.
- 16 Yeo W, Chan PK, Hui P, *et al.* Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol* 2003;70:553–61.
- 17 Weinbaum CM, Mast EE, Ward JW. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *Hepatology* 2009;49(5 Suppl):S35–44.
- 18 Artz AS, Somerfield MR, Feld JJ, *et al.* American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol* 2010;28:3199–202.
- 19 Zon RT, Neuss MN. ASCO provisional clinical opinion: chronic hepatitis B virus infection in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Oncol Pract* 2010;6:193–4.
- 20 Day FL, Karnon J, Rischin D. Cost-effectiveness of universal hepatitis B virus screening in patients beginning chemotherapy for solid tumors. *J Clin Oncol* 2011;29:3270–7.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow