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LESSON OF THE MONTH

Lesson of the month 2: Severe reactivation of hepatitis B after immunosuppressive chemotherapy

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ABSTRACT

Patients with current or past hepatitis B virus (HBV) infection are at risk of viral reactivation if they receive immune-modulating treatment or chemotherapy. This can range from subclinical elevation in HBV DNA levels, to abnormal liver function tests, to severe hepatitis with liver failure and risk of death. All patients should be screened for hepatitis B with surface antigen and core antibody before receiving immunosuppression. Patients with positive hepatitis B serology should be referred for specialist advice. Prophylactic antiviral treatment is recommended for patients with current/past hepatitis B who receive immunosuppressive chemotherapy.

KEYWORDS: Hepatitis B, reactivation, immunosuppression, chemotherapy, antiviral therapy.

Introduction

Patients with current or past hepatitis B virus (HBV) infection are at risk of viral reactivation if they receive immune-modulating treatment or chemotherapy. This can range from subclinical elevation in HBV DNA levels to abnormal liver function tests (LFTs), to severe hepatitis with liver failure and risk of death.

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Case report

A 72-year-old man was noted to have submandibular gland swelling at a dental appointment. Further assessment showed widespread lymphadenopathy and excision biopsy diagnosed diffuse large B-cell lymphoma. His past medical history included pulmonary embolus.

He was planned for six cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine, prednisolone). Before starting treatment, hepatitis B serology was checked; he was anti-HBcAb (hepatitis B core antibody) positive, HBsAg (hepatitis B surface antigen) negative, anti-HBsAb (hepatitis B surface antibody) negative with undetectable HBV DNA (<20 IU/ml), in keeping with past HBV infection. LFTs were normal. The virology report stated: 'consistent with past HBV infection, but risk of reactivation on immunosuppression. Please ensure HBsAg and LFTs are monitored.'

After four cycles of R-CHOP (January 2013), tests for HBsAg were positive and HBV DNA was 1.2×10^7 IU/ml, consistent with acute HBV reactivation. The patient was started on tenofovir 245 mg daily.

He completed six cycles in March 2013 and positron emission tomography computed tomography (PET-CT) confirmed good radiological response. However, in May 2013 he was admitted with jaundice and international normalised ratio (INR) >10. Blood tests showed significant liver dysfunction (bilirubin 105 µmol/l, alanine aminotransferase [ALT] 988 U/l, alkaline phosphatase [ALP] 317 U/l and albumin 35 g/l). HBV DNA had fallen to 5,300 IU/ml. An abdominal CT scan showed no biliary obstruction or other cause for jaundice. Tests for other hepatotropic viruses were negative. Transjugular liver biopsy showed markedly cholestatic hepatitis (modified histology activity index [HAI] inflammatory grade 9/18 and fibrosis

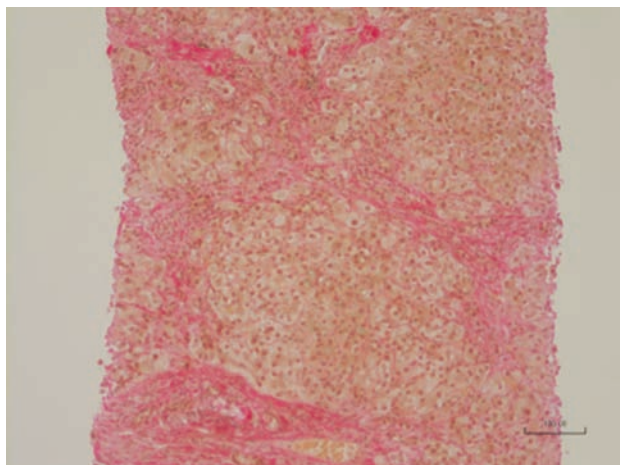


Fig 1. Liver biopsy showing markedly cholestatic hepatitis (modified histology activity index [HAI] inflammatory grade 9/18 and fibrosis stage 5/6) in keeping with fibrosing cholestatic hepatitis B.

Key points

- > Patients with current or past hepatitis B (HBV) infection are at risk of viral reactivation if they receive immune-modulating treatment or chemotherapy
- > Reactivation can range from subclinical elevation in HBV DNA levels, to severe hepatitis with liver failure and death
- > All patients should be screened for hepatitis B with surface antigen and core antibody before receiving immunosuppression
- > Patients with positive hepatitis B serology should be referred for specialist advice
- > Prophylactic antiviral treatment is recommended for patients with current/past hepatitis B who receive immunosuppressive chemotherapy

stage 5/6), in keeping with fibrosing cholestatic hepatitis B (Fig 1). He was started on lamivudine in addition to tenofovir, but his clinical condition deteriorated (bilirubin 366 $\mu\text{mol/l}$, albumin 31 g/l). He required prolonged hospital admission (3 weeks) complicated by poor nutrition and pruritis. Fig 2 shows a graph of his blood tests during the HBV reactivation. His LFTs gradually improved and normalised after 5 months. He is now clinically well and remains on tenofovir.

Discussion

The use of rituximab (and other immunosuppressants) is increasing for various autoimmune, haematological and oncological conditions. The purpose of presenting this case is to raise awareness of this potentially life-threatening complication for clinicians who prescribe rituximab and other immunosuppressants. Due to the risk of HBV reactivation with

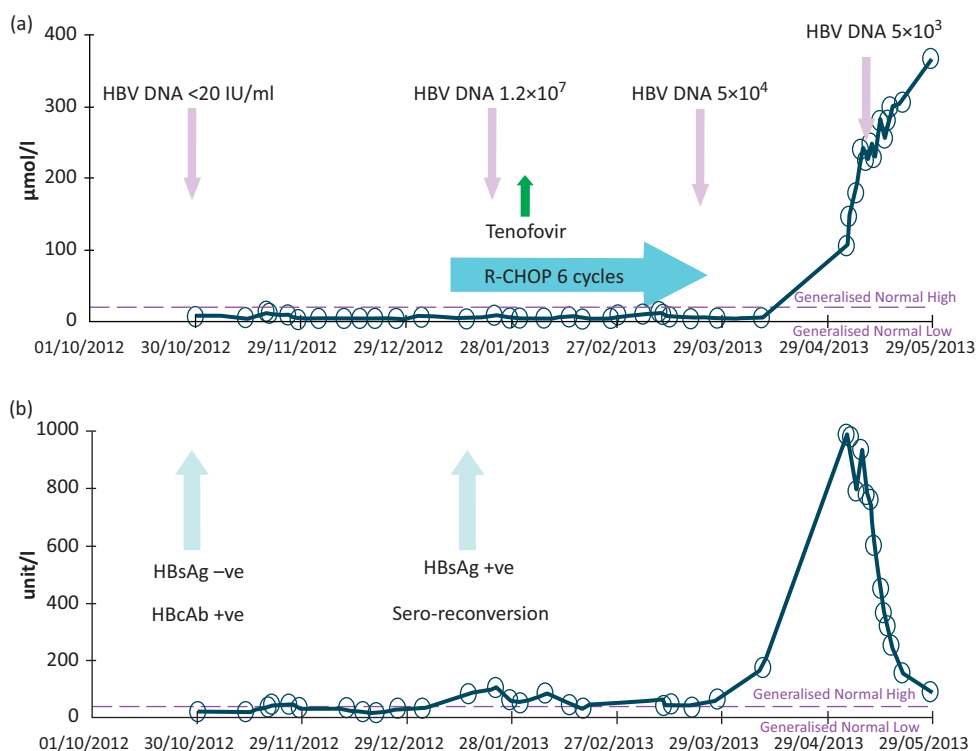


Fig 2. Patient's blood results during the hepatitis B virus (HBV) reactivation. (a) Bilirubin and (b) alanine aminotransferase (ALT). HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; R-CHOP = rituximab, cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine, prednisolone.

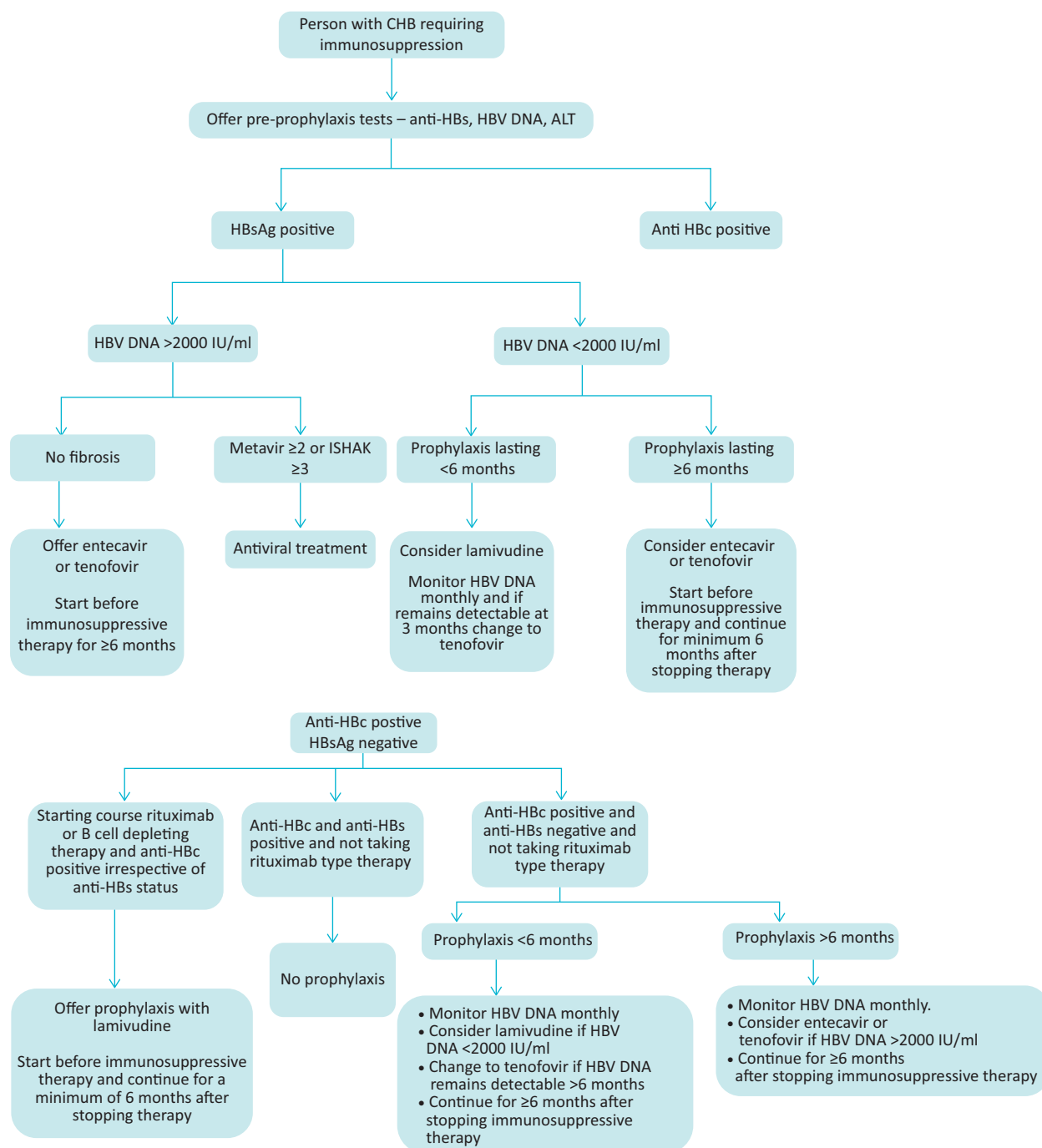


Fig 3. Recommendations of the National Institute for Health and Care Excellence (2013) for the management of hepatitis B in patients receiving immunosuppression and chemotherapy. ALT = alanine aminotransferase; CHB = chronic hepatitis B; Anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; Anti-HBs = hepatitis B surface antibody.

immunosuppression, international guidelines recommend screening all patients for HBsAg and anti-HBcAb before initiating treatment to identify 'at-risk' patients^{1,2} who can be actively monitored or given prophylaxis. Despite these recommendations, HBV screening remains sporadic, with one large US series showing that only 16% of 18,688 patients were screened before chemotherapy.³ Studies assessing HBV

screening practices of oncologists suggest that 20–47% of oncologists do not routinely screen for HBV before treatment, 20% never screen and others screen 'high-risk' individuals.^{4,5} Zurawska *et al*⁶ developed a decision model to compare clinical outcomes, costs and cost-effectiveness of three HBV screening strategies for patients receiving R-CHOP. Screening all patients was the least costly and associated with the highest 1-year

survival rate (compared with screening 'high risk' and 'none'). Worldwide, chronic HBV infection is very common⁷ and importantly a high proportion of patients with current or past HBV infection are unaware of the infection,⁸ so it is important to screen all patients who receive immunosuppression/chemotherapy.⁹

In this case, HBV screening was undertaken before starting R-CHOP and the patient was anti-HBcAb positive, but HBsAg negative, in keeping with past infection. The decision was made to monitor for reactivation with LFTs, HBsAg and HBV DNA testing during chemotherapy, as per the guidelines of the European Association of the Study of the Liver (EASL). After 3 months, blood tests showed HBsAg positivity and high HBV DNA, suggesting active HBV. Patients who have had past HBV infection can reactivate because covalently closed, circular HBV DNA (cccDNA) is archived in hepatocyte nuclei and remains under immune control,¹⁰ although in states of immunosuppression viral replication can occur, leading to production of HBV DNA and HBsAg and subsequent HBV reactivation.

When this patient showed serological evidence of HBV reactivation he was treated with tenofovir to suppress viral replication, but 2 months later, after chemotherapy was complete, he developed a very severe fibrosing cholestatic hepatitis. Importantly, the consequences of HBV reactivation (severe hepatitis) frequently occur after completion of chemotherapy when immune reconstitution occurs and the cytotoxic T-cell-mediated response is restored.¹¹ HBV reactivation can occur anywhere from 2 weeks to more than 1 year after cessation of immunosuppression.⁹ Therefore, ongoing monitoring of patients is essential after chemotherapy, even if they are started on antiviral therapy.

There are many immunosuppressive and chemotherapeutic agents and the absolute risk of HBV reactivation varies with specific regimens,^{9,11} although few studies have assessed risks with specific agents. Overall, studies suggest a reactivation rate of approximately 50% for HBsAg-positive patients receiving chemotherapy for lymphoma and 15% for solid tumours.^{12–16} Patients with past infection (anti-HBcAb positive only) have lower reactivation rates (approximately 5%).^{17,18} More intensive immunosuppressive regimens, particularly those including rituximab and/or high-dose steroids, are the highest risk.^{9,11} Recent studies suggest that reactivation rates in anti-HBcAb-positive patients treated with rituximab are 25%.^{19,20} The clinical significance of HBV reactivation can be variable, ranging from a mild transaminitis to liver failure and death. Severe reactivation resulting in jaundice occurs in 10–22% of patients and has a high mortality rate of 4–41%.^{12,13,15,21,22} As well as being a life-threatening complication, the medical resource costs of HBV reactivation can be significant, as in this case.

Importantly, HBV reactivation in HBsAg- or anti-HBcAb-positive patients can be prevented by prophylactic treatment with oral antiviral drugs.^{23,24} Studies have shown that prophylactic antiviral therapy before starting immunosuppression is more effective at preventing hepatitis and reduces mortality compared with initiating treatment once reactivation has occurred.^{23,24} As a result, EASL and the National Institute for Health and Care Excellence (NICE) guidance advises prophylactic antiviral therapy for

all HBsAg-positive patients who undergo treatment with immunosuppression or chemotherapy,² and treatment should be continued for at least 6 months after completion of immunosuppressive therapy.²⁵ NICE guidelines (Fig 3) recommend treatment with lamivudine if HBV DNA is <2,000 IU/ml and the immunosuppression/chemotherapy will last <6 months.²⁶ For patients whose HBV DNA is >2,000 IU/ml, or who will receive immunosuppression/chemotherapy for >6 months, entecavir or tenofovir treatment is recommended.

For anti-HBcAb-positive/HBsAg-negative patients receiving immunosuppression/chemotherapy, EASL guidelines recommend ALT and HBV DNA monitoring 1- to 3-monthly and antiviral therapy to be started if the HBV DNA increases.² Our patient was managed according to these recommendations. However, in view of increasing evidence of the high risk of reactivation in anti-HBcAb-positive patients with rituximab, the new NICE guidelines that were published after this patient presented recommend prophylactic treatment with lamivudine.²⁵ If our patient had been managed according to these guidelines his reactivation might have been prevented. For anti-HBcAb-positive patients who receive immunosuppressive regimens without rituximab, NICE guidelines recommend monitoring HBV DNA levels monthly and treating with antivirals if HBV DNA increases.²⁵

Conclusion

This case highlights the importance of HBV testing in patients receiving immunosuppression or chemotherapy to identify patients at risk of HBV reactivation, and to treat patients who have current or past HBV infection prophylactically with antiviral therapy to prevent reactivation and the associated morbidity and mortality. ■

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