


Hepatitis B Virus Reactivation Following Treatment of HNSCC With Cisplatin

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Abstract

Hepatitis B Virus (HBV) reactivation is a known complication of intense immunosuppression with B-cell depleting monoclonal antibody therapy and transplantation immunosuppression. HBV reactivation has occurred following treatment with chemotherapy regimens for hematologic malignancies and solid tumors. There are 2 prior case reports of HBV reactivation following cisplatin monotherapy for head and neck squamous cell carcinoma (HNSCC). Here, we present a case of a 49-year-old Caucasian male with a past medical history of laryngeal squamous cell carcinoma (SCC). There are no consensus guidelines on how to define hepatitis B reactivation. There are guidelines on when to initiate prophylaxis with Entecavir while on immunosuppressive therapy with risk according to medication category and hepatitis B surface antigen/hepatitis B core antibody IgG serology. CDC recommends screening everyone. American Society of Clinical Oncology (ASCO) now with a recent update in 2020 recommends screening everyone. There is a definite role of immunosuppression in HBV reactivation, however, there is also direct enhancement by cisplatin of viral replication by creating endoplasmic reticulum stress which increases HBV DNA indirectly. Finally, cytotoxicity enhances HBV reactivation and immune reconstitution post withdrawing immunosuppressive treatment. Because of the effects of chemotherapy, aka cisplatin goes beyond immunosuppression-related reactivation of HBV, our recommendations are in line with CDC and ASCO to screen all patients for HBV before onset of chemotherapy and start Entecavir/Tenofovir Disoproxil Fumarate before the onset of chemotherapy for HBV-positive patients.

Keywords

infectious disease, gastroenterology, hematology oncology

Introduction

Guidelines for hepatitis B screening are well described in transplant recipients and those undergoing chemotherapy for hematologic malignancies. However, the American Society of Clinical Oncology did not recommend routine screening in patients undergoing chemotherapy for solid organ malignancies who are not high risk in 2010.^{1,2} Therein lies the risk of reactivation with its associated morbidity in average-risk patients who may have clinically silent hepatitis B undergoing chemotherapy for solid organ tumors. However, hepatitis B reactivation may be a silent event in itself only detected by routine laboratory monitoring completed during chemotherapy.

Hepatitis B reactivation is notoriously difficult to define. There are no current consensus guidelines on how to identify hepatitis B reactivation.³ However, some studies use either a 10-fold increase of HBV DNA from normal or de novo detection of serum HBV DNA compared to baseline as

evidence of reactivation.⁴ Another study cited an alanine aminotransferase (ALT) increase more than 3 times normal.³ While there are also guidelines for screening high-risk patients with a known history of hepatitis B, there is also risk stratification according to the chemotherapy regimen used. In the 2015 edition of the American Gastroenterological Institute, Technical Review on Prevention and Treatment of hepatitis B Virus Reactivation During Immunosuppressive

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Drug Therapy, the only cytotoxic chemotherapy drugs classified with risk are those of the anthracycline class; doxorubicin and epirubicin, which are classified low risk and high risk according to HBsAg positivity and hepatitis B core antibody IgG positivity.³ The review further recommends use of nucleotide analogue Entecavir or Tenofovir Disoproxil Fumarate in these patients prior to onset of chemotherapy which is crucial to prevent reactivation, hepatitis B flare, or worsening hepatitis B. This case represents a patient with a prior unknown history of hepatitis B who was diagnosed with HNSCC of the larynx, treated with cisplatin and radiation therapy who developed reactivation characterized by ALT greater than 3 times normal and HBV DNA > 8.23 log IU/mL. The patient further developed worsening hepatitis and manifested decompensated cirrhosis with clinically significant portal hypertension over the next year manifested by refractory ascites and evidence of varices, splenomegaly, and cirrhosis on computed tomography (CT) of the abdomen and pelvis. This case also firmly establishes why the updated ASCO 2020 guidelines Clinical Opinion on hepatitis B should be followed by screening everyone prior to start of chemotherapy, so Entecavir can be started pre-emptively preventing complications of hepatitis B reactivation such as decompensated cirrhosis or acute liver failure.

Case Description

A 49-year-old Caucasian male with a past medical history of recently diagnosed laryngeal cancer with completion of 3 cycles of chemotherapy with cisplatin and radiation treatment presented with yellowing of the skin due to jaundice and fatigue during a regularly scheduled appointment. He was subsequently hospitalized after further workup revealed a transaminase of 305 and bilirubin of 2.8. An acute hepatitis panel revealed the patient to be hepatitis B surface antigen-positive, hepatitis B e antigen-positive, hepatitis B core IgM negative, and positive HBV DNA > 8.23 log IU/mL. With the presence of the positive serologic markers, HBV DNA > 8.23 log IU/mL, and recent elevation of aspartate transaminase (AST) and ALT > 3 times the upper limit of normal, a presumptive diagnosis of hepatitis B reactivation was made. Other causes of liver dysfunction were also ruled out. Alpha-1-antitrypsin was negative. A fourth-generation human immunodeficiency virus (HIV) antigen/antibody combination test, hepatitis C antibody, and hepatitis A IgM were all negative. Hepatitis A IgG was positive consistent with prior infection or vaccination. He had a normal ferritin level with normal transferrin saturation ruling out hemochromatosis. Right upper quadrant ultrasound imaging did not reveal any evidence of cirrhosis. Anti-mitochondrial antibody testing was negative, as was the antinuclear antibody (ANA). He had a mildly positive anti-smooth muscle antibody titer 1:40. The patient had normal ALT at baseline. A hepatitis panel was not initially checked. It was not indicated given his low risk status at the time per ASCO guidelines in 2010.² Body

mass index (BMI) was 21.5. He did not have an ultrasound nor imaging of the liver as it was not indicated at the time. After treatment for his underlying condition with cisplatin and radiation for HNSCC, he underwent esophagogastroduodenoscopy (EGD) for percutaneous endoscopic gastrostomy (PEG) tube placement due to cachexia and radiation treatment, and there was no evidence of clinically significant portal hypertension. This patient underwent 3 positron emission tomography (PET) scans from the skull base to the mid-thigh, which was negative for metastatic disease obtained at 3 months after treatment with cisplatin and concurrent chemoradiation, and 6 months thereafter. Thus, no stigmata of clinically significant liver disease at baseline before the presumptive diagnosis of hepatitis B reactivation was made. However, due to the patient's nonadherence to follow-up, after the withdrawal of cisplatin, his liver function deteriorated into decompensated liver cirrhosis with clinically significant portal hypertension within the next several months to a year with evidence of ascites, splenorenal shunting, and nodular cirrhotic liver on CT of abdomen and pelvis. His transaminases were frequently found to be elevated at 300-400 over the next year. He began to show progressive signs of decompensation with coagulopathy and massive ascites. Two years after his initial HBV DNA level was drawn, he was positive for hepatitis B surface antigen, hepatitis B e antigen, with the new addition of hepatitis B Core IgM suggesting possible acute exacerbation of hepatitis B. His hepatitis B DNA level was 8.603 log IU/mL. 20-27.5% of patients with an acute exacerbation of hepatitis B are positive for the IgM hepatitis B Core Antibody.⁵ This patient was eventually referred for possible liver transplant due to decompensated cirrhosis to tertiary center. He was started on Entecavir at the time of the acute exacerbation of hepatitis B. One month after he began therapy, his HBV DNA viral load was 8.08 log IU/mL. He was still positive for the hepatitis B core antibody IgM and hepatitis B surface antigen. Three months after starting treatment for hepatitis B, he was found to have a markedly reduced HBV DNA viral load of 5.23 log IU/mL. One year posttreatment follow-up, he had reverted to anti-hepatitis B core antibody IgG with Hepatitis B surface antigen positivity. His care was transferred to a tertiary care center for liver transplant evaluation and he subsequently passed away. Entecavir was started later in the course because the patient did not require continued inpatient admission while critical labs such HBV DNA and hepatitis B e antigen were pending. He was finally started on Entecavir with decompensated cirrhosis in hospital later in the course when his decompensated cirrhosis required longer inpatient monitoring, but he was nonadherent with therapy in the outpatient due to cost.

Discussion

There are no consensus guidelines on how to define hepatitis B reactivation. There are guidelines on when to initiate

prophylaxis with immunosuppression with risk graded according to medication category and hepatitis B surface antigen/hepatitis B core antibody IgG serology. This patient did not have clinically evident manifestations or biochemical manifestations of possible underlying hepatitis B before chemotherapy for solid organ tumor, nor did he have a risk profile that would warrant checking or preemptively treating him to prevent a potential hepatitis B flare or reactivation.³ However, some studies report higher rates of hepatitis B reactivation with cisplatin use, though the numbers in this particular study were small.⁶ The CDC recommends hepatitis B screening before all chemotherapy begins.⁷ As discussed above, the American Society of Clinical Oncology (ASCO) cited insufficient evidence to make a recommendation for the average-risk population.¹ The American Gastroenterological Society recommends screening only those at high risk.³ In November 2020, ASCO updated this guideline with a clinical opinion to screen all patients undergoing systemic anticancer therapy with hepatitis B core IgG, hepatitis B surface antigen, and hepatitis B surface antibody.² This patient did not report a prior history of IV drug abuse. He was HIV and hepatitis C negative. The patient is heterosexual and did not engage in any high-risk behavior. Regardless, this case demonstrates support for the new clinical guideline as our patient did not fit the risk profile of the typical person to screen for hepatitis B per 2010 ASCO guidelines at the time. If CDC guidelines were followed, he could have been placed on Entecavir prophylaxis. He could still be potentially living today while having been able to tolerate the immunosuppression induced by his cisplatin. However, this may not only be related to underlying immunosuppression. This may be due in part to direct enhancement of viral replication by cisplatin itself. The endoplasmic reticulum is an intracellular organelle that is involved in lipid and protein synthesis. Cisplatin creates endoplasmic reticulum stress by upregulating Hepatic Nuclear Factor-4 alpha and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1 α) which bind to a core promoter and enhancer II region of the HBV genome upregulating transcription thus increasing HBV DNA levels in HBV replicating cells and an HBV transgenic mouse model.⁸ Autophagy plays a central role in cisplatin-induced HBV replication as well by promoted HBV replication and autophagy through ROS/JNK and AKT/mTOR signaling.⁹ Finally, chemotherapy promotes HBV reactivation via immune dysfunction through cytotoxic damage to rapidly dividing lymphocytes/granulocytes. This, in turn, allows HBV replication to increase without causing overt hepatotoxicity. It is the cytotoxic response following immune reconstitution that induces hepatic inflammation and toxicity once the chemotherapeutic agent is withdrawn.¹⁰ These findings collectively may help to explain why our patient developed a hepatitis flare during chemotherapy due to direct stimulatory effects of cisplatin on HBV replication followed by continued inflammation manifesting quickly as decompensated cirrhosis in the

year following chemotherapy withdrawal due to immune reconstitution. To our knowledge, this is the second described case of hepatitis B reactivation based solely on the use of cisplatin for the treatment of solid organ tumors. The only known case associated with solely cisplatin or other platinum was published which detailed treatment of cervical cancer with chemotherapy with cisplatin and radiation but also involved carboplatin.¹¹ There is another case described which details a patient with pancreatic cancer and liver metastases treated with cisplatin and gemcitabine.¹² Most important is to start Entecavir as soon as hepatitis B reactivation is diagnosed or prior to start of immunosuppression including chemotherapy per AGA guidelines.³ The new Clinical Opinion published in 2020 on hepatitis B screening from ASCO can help to identify these patients prior to chemotherapy to decrease morbidity associated with hepatitis B reactivation in patients undergoing chemotherapy for solid tumors regardless if they contain an anthracycline or not.

Recommendations

We suggest and would follow with CDC and the new updated ASCO opinion to screen everyone before the start of chemotherapy for any malignancy with hepatitis B surface antigen and hepatitis B core antibody IgG serology to find those who would benefit from further monitoring and treatment of reactivation Entecavir or Tenofovir Disoproxil Fumarate since it can be associated with significant morbidity and mortality.

Authors' Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in the article.

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