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# Liver Failure After Chemotherapy: Did We Forget Something?

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## The Case

A 51-year-old Cantonese-speaking female with a history of stage 3 breast cancer had been receiving neoadjuvant chemotherapy. Of note, the oncology service had checked her liver function tests prior to chemotherapy, and they were found to be normal. Hepatitis serologies were not checked prior to administration of chemotherapy. Well into receipt of her chemotherapy, the patient complained of fever, rash, and bone pain and was subsequently admitted to the general medicine service. Admitting labs were notable for a mild transaminitis, but repeat testing of liver function tests was not performed during this hospitalization nor were hepatitis serologies checked. Cultures of blood and urine were negative, and her symptoms were attributed to pegfilgrastim (fever, bone pain) and paclitaxel (rash). Two days later, the patient presented with abdominal pain and AST of 9986 U/L, ALT 4366 U/L, and an INR of 2.3. Shortly thereafter, she became encephalopathic, requiring endotracheal intubation. Subsequent review of her outside records revealed chronic hepatitis B, diagnosed 15 years earlier, with surface antigen positivity. The patient had no knowledge of her hepatitis B diagnosis. The patient was started on entecavir for her reactivation of hepatitis B and transferred to a liver transplant center. Luckily, she has made a complete recovery from her liver failure and is receiving chronic therapy for her hepatitis B, along with treatment for her breast cancer.

Analysis of the case revealed that the oncology department lacked a standard practice to check hepatitis serologies on patients prior to initiation of chemotherapy. Moreover, the admitting team erred by not considering the possibility of hepatitis as the cause of the patient's fever, rash, and transaminitis.

## The Commentary

Hepatitis B virus (HBV) reactivation following chemotherapy is an important, but often overlooked, complication of chemotherapy in patients at risk of hepatitis B infection. This condition can be prevented by screening all potential recipients of chemotherapy with hepatitis B serology and providing prophylactic

antiviral therapy prior to cancer chemotherapy in those at risk of hepatitis B reactivation.

The patient in question is a Cantonese-speaking woman likely to have been born in a region with high hepatitis B endemicity. Hepatitis B reactivation occurs more commonly in the setting of chronic hepatitis B with positive hepatitis B surface antigen (HBsAg) serology. However, it may also occur in the setting of past exposure to hepatitis B, when the only positive serological marker may be the hepatitis B core antibody (HBcAb). Under such circumstances, a patient may undergo reverse seroconversion or *seroreversion,* whereby the patient's serology changes from HBsAg negative to HBsAg positive. While uncommon, seroreversion can occur with more intense chemotherapy regimens, especially regimens for hematological malignancies using rituximab.

Screening patient prior to chemotherapy

A number of national and international organizations recommend screening patients for HBV prior to cancer chemotherapy, especially patients at high risk.(1-4) This includes all individuals born in areas of high or intermediate prevalence and specifically all countries within Asia (Table). The regional prevalence of chronic HBV varies widely. In areas of high endemicity in the Asia-Pacific region, this rate approaches 20%; whereas, in Australia less than 1% of the population are HBsAg positive.(5-7) Screening for current and past hepatitis B infection can readily be performed with HBsAg and HBcAb qualitative testing, respectively. Patients with current infection (HBsAg positive) should also have HBV viral loads quantified and aminotransferase testing to identify those patients who might benefit from long-term antiviral therapy.

HBV reactivation

Patients who have been infected with HBV are vulnerable to disease reactivation during immunosuppressive pharmacotherapy.(8) The clinical consequences vary from asymptomatic elevation of hepatic enzymes to severe hepatitis and death from fulminant hepatic failure. In addition to the direct harm caused by HBV reactivation, patient care may be compromised because of the need to delay or prematurely cease chemotherapy.(9)

The clinical presentation of HBV reactivation can range from asymptomatic anicteric elevation of hepatic enzymes to fulminant hepatitis. However, other causes of hepatitis must be excluded, including chemotherapy-induced hepatic injury, tumor infiltration of the liver, and concurrent infection with other viruses, such as hepatitis A, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). Rarely, hepatitis may be caused by tumor obstruction of the hepatic veins producing the Budd-Chiari syndrome. In this patient, the cause of the initial elevation in transaminases was not completely explored. Thorough assessment would have revealed both positive HBsAg and a detectable viral load, resulting in the initiation of antiviral therapy. Antiviral therapy may have prevented the patient's progression to acute liver failure.

Incidence and risk factors for HBV reactivation

The risk for HBV reactivation is influenced by both the type of malignancy and selected chemotherapeutic agent. In patients receiving chemotherapy breast cancer, the rate of HBV reactivation ranges between 41% and 56%.(9,10) Given the high risk for HBV reactivation in this setting, the oncologists should have been aware of the importance of screening for HBV. For other solid tumors, the rate of reactivation appears to be lower, ranging between 14% and 21%.(11-13) Patients with lymphoma are particularly at risk.(12,14)

Reinforcing this point, reactivation rates of 48% have been reported in HBsAg-positive patients treated with chemotherapy for lymphoma.(15)

Timing and choice of antiviral therapy

The risk of reactivation can be greatly reduced by identifying at-risk patients prior to chemotherapy and utilizing prophylactic antiviral therapy. Lamivudine has proven efficacy and safety in preventing HBV reactivation following chemotherapy for both hematological and solid malignancies. However, a major concern with its prolonged use is the emergence of resistance mutations in the YMDD region of the HBV DNA polymerase. Cases of severe HBV reactivation hepatitis and hepatic decompensation have been reported following development of lamivudine resistance.(16) Alternative antiviral agents such as adefovir, entecavir, or tenofovir are likely as effective as lamivudine in preventing HBV reactivation and have a significantly lower resistance rates.

Concluding remarks

Intensive cytotoxic chemotherapy may allow reactivation of hepatitis B in patients who are currently infected or even those who have apparently cleared the virus (HBsAg negative, HBcAb positive). Following chemotherapy, restoration of the patient's immune system can result in a hepatitis B flare with significant hepatic necroinflammation and liver failure, as demonstrated in this case. Consequently, hepatitis B serology must be checked prior to initiation of immunosuppressive chemotherapy. The risk for reactivation of hepatitis B depends on the type of chemotherapy and is, therefore, indirectly associated with the type of malignancy. The more intensive chemotherapeutic regimens for hematological malignancy and breast cancer are particularly predisposed. However, case reports of hepatitis B reactivation have been reported even with relatively mild immunosuppression such as corticosteroids, methotrexate, and infliximab. Although the risk is likely considerably lower, it is still advisable to check hepatitis B serology in all patients with risk factors for HBV infection. The patient described in this case report experienced a complication of chemotherapy that could have been avoided with appropriate screening, and oncology units should have protocols in place to prevent such mishaps from occurring.

Take-Home Points

- Remember to screen for hepatitis B infection in populations that are at risk (Table).
- Screening should entail testing for hepatitis B surface antigen (HBsAg) and core antibody (HBcAb).
- Patients with chronic infection may qualify for long-term antiviral therapy and should have HBV viral load quantification and baseline aminotransferase tested. An opinion should be sought from a specialist with regard to choice of antiviral therapy and duration.
- Cancer chemotherapy and other immunosuppressive therapies can result in reactivation of hepatitis B with catastrophic consequences to the patient if antiviral therapy is not started.
- Intensely immunosuppressive regimes may even allow *seroreversion* of patients who have apparently cleared hepatitis B. Patients receiving rituximab or those treated for haematological malignancies and breast cancer appear to be particularly at risk.
- Prophylactic antiviral therapy prevents HBV reactivation and is generally safe and well tolerated.
- Treating established HBV reactivation is less effective than prophylactic therapy.
- Duration of antiviral therapy depends on chemotherapy and restitution of the host's immunity.

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## Table

Table. Groups at high risk of HBV who should be screened (from AASLD guidelines [1])

**Individuals born in areas of high or intermediate prevalence for HBV including immigrants and adopted children:**

- Asia: All countries
- Africa: All countries
- South Pacific Islands: All countries
- Middle East (except Cyprus and Israel)
- European Mediterranean: Malta and Spain
- The Arctic (indigenous populations of Alaska, Canada, and Greenland)
- South America: Ecuador, Guyana, Suriname, Venezuela, and Amazon, regions of Bolivia, Brazil, Columbia, and Peru
- Eastern Europe: All countries except Hungary
- Caribbean: Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St Kitts and Nevis, St Lucia, and Turks and Caicos
- Central America: Guatemala and Honduras

**Other groups recommended for screening:**

- US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity
- Household and sexual contacts of HBsAg-positive patients
- Persons who have ever injected drugs
- Persons with multiple sexual partners or history of sexually transmitted disease
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT or AST
- Patients undergoing renal dialysis
- All pregnant women
- Persons needing immunosuppressive therapy

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