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Hepatitis B Reactivation in a Patient Receiving Chemotherapy for Breast Cancer: A Case Report

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Abstract. *Hepatitis B virus (HBV) reactivation is a known complication of immunosuppressive therapy. While patients who are undergoing treatment with anti-CD20 agents or stem cell transplantation are commonly screened for chronic HBV infection prior to treatment, there are no consensus guidelines regarding HBV screening for patients undergoing chemotherapy for solid tumors. We present a rare case of fulminant liver failure due to HBV reactivation in a patient receiving chemotherapy for breast cancer. Our case highlights the importance of developing definitive guidelines regarding HBV screening in patients receiving chemotherapy for solid tumors and raises the question of the need for universal screening.*

Between 5-10% of the world's population (or approximately 350 million persons) are chronically infected with hepatitis B virus (HBV) (1, 2). In the United States, the prevalence of chronic HBV infection is lower (approximately 0.5% of the general population) but can be as high as 10% in some immigrant populations (2). The Centers for Disease Control estimates the number of chronic cases of HBV to be up to 1.4 million in the United States (3). This number may even be higher as over 60% of patients may be unaware of their HBV infection (4, 5).

HBV reactivation is recognized as a complication that may occur in patients undergoing chemotherapy with B-cell-depleting agents or stem cell transplantation (6, 7). Screening for hepatitis B is recommended in these patients and is commonly done in clinical practice (5). There are no clear guidelines regarding screening of patients receiving chemotherapy for solid tumors and there are limited epidemiological data on the risk of HBV reactivation in these patients. Although reactivation may be asymptomatic, it can lead to hepatitis, liver failure, treatment interruptions, and even death (6, 7).

We present a case report of fulminant liver failure due to HBV reactivation in a patient receiving chemotherapy for breast cancer, highlighting the importance of considering viral status prior to initiation of routine treatment for solid organ tumors.

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Case Report

A 58-year-old female with no significant past medical history noticed a mass in her right breast during self-examination. Physical examination revealed peau d'orange appearance of the right breast. She underwent a bilateral diagnostic mammogram and ultrasound, which revealed a 2.2×1.8×2.4 cm irregular mass with ill-defined margins, with diffuse right breast skin thickening measuring up to 0.7 cm. Multiple axillary nodes were visualized, with the most suspicious measuring 1.2×0.2×1.3 cm. The patient underwent percutaneous imaging-guided core biopsy with pathology consistent with infiltrating moderately differentiated ductal carcinoma, with metastatic carcinoma to the right axillary node. Further testing revealed estrogen receptor-positive, progesterone receptor-positive, human epidermal growth factor receptor 2/neu-negative tumor. Computed tomography (CT) of the chest, abdomen and pelvis was performed without evidence of distant metastatic disease. Final staging was cT4dN1M0.

As the patient presented with inflammatory breast cancer, neoadjuvant chemotherapy with dose dense adjunctive chemotherapy (60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide) followed by 175 mg/m^2 paclitaxel was planned with curative intent. She completed four cycles of adjunctive chemotherapy without unexpected side-effects, and proceeded to cycle 1 of paclitaxel therapy. Twelve days following administration of paclitaxel, the patient was admitted to the hospital with abdominal pain, nausea, vomiting, and dark urine for several days. Her laboratory work-up revealed

hyperbilirubinemia (total bilirubin: 13.7 mg/dl, direct bilirubin: 7.8 mg/dl), elevated transaminases (aspartate aminotransferase: 9,328 U/l, alanine aminotransferase: 6,079 U/l), and coagulopathy (international normalized ratio: 3.4). CT of the abdomen and pelvis was negative for acute abnormalities, and the liver appeared unremarkable. Right upper quadrant ultrasound showed unremarkable spectral Doppler interrogation of the hepatic vasculature. Work-up revealed positivity for hepatitis B surface antigen and hepatitis B core antibody, with quantitative HBV reverse transcription polymerase chain reaction of 1,548,021 IU/ml. The patient had no known history of hepatitis B or liver disease. She was subsequently started on tenofovir.

The patient began to develop worsening encephalopathy and eventually became minimally responsive, requiring endotracheal intubation. CT of the head revealed brain edema. Her clinical status continued to decline, with worsening coagulopathy and renal failure. As she was deemed to not be a liver transplant candidate due to active breast cancer with nodal involvement, her family elected to pursue comfort care. The patient eventually died 12 days after initial presentation.

Discussion

Reactivation of HBV infection is recognized as a complication of immunosuppressive therapy (6, 7). In a meta-analyses by Paul *et al*. (9), HBV reactivation in patients receiving solid tumor chemotherapy regimens without anti-viral prophylaxis ranged from 4-68% (median 25%) in those with chronic HBV infection, and 0.3-9% in those with resolved HBV infection. Prophylaxis reduced the risk for HBV reactivation to 3.5% in those with chronic HBV infection. Prophylaxis also reduced the incidence of HBV-related hepatitis, and chemotherapy interruptions.

Numerous societies have published guidelines on HBV screening recommendations in patients undergoing immunosuppressive therapy. Guidelines range from a universal screening strategy to a risk-adapted approach. In 2015, the American Society of Clinical Oncology released a provisional clinical opinion update regarding HBV screening (5). They recommended that all patients undergoing anti-CD20 therapy or hematopoietic cell transplantation should be screened for HBV infection. For all other patients, they introduced a risk-adaptive strategy to identify and treat those with HBV infection. Risk factors included patients born in a country with more than 2% HBV prevalence, parents born in high-prevalence region, household or sexual contact with HBV-positive individuals, human immunodeficiency virus-positive status, injection drug use, and men who have sex with men. While these guidelines highlight a growing awareness of hepatitis B reactivation as a complication of chemotherapy administration, it may still miss a proportion of chronic hepatitis B cases through its risk-adapted strategy (10). The National Comprehensive Cancer Network similarly recommends that all patients should be assessed for risk factors of HBV infection and those with risk factors should be screened (11). But in contrast, it also recommends that if risk-based screening cannot be implemented, then consideration should be made for universal screening. Numerous other societies including the Centers of Disease Control and Prevention and the European Society for Medical Oncology recommend screening for HBV infection in all patients receiving immunosuppressive therapy (2, 5, 12, 13).

Despite these recommendations, fewer than 20% of oncologists screen for HBV infection prior to initiating chemotherapy (14). In 2011, the MD Anderson Cancer Center conducted a retrospective study examining HBV screening rates in patients newly diagnosed with cancer (15). In patients undergoing intravenous chemotherapy at their institution, the HBV screening rate was 16.2%. Of those with risk factors for HBV infection, fewer than 19% were screened.

Furthermore, there are uncertainties regarding which solid tumor chemotherapy regimens are at risk for reactivating HBV. There have been several case reports of HBV reactivation among patients undergoing anthracycline-based chemotherapy (1, 8), as our patient received. One meta-analyses found the risk of reactivation among anthracycline based chemotherapy regimens to be 29% (14-88%) (9). Even prolonged courses of steroids have been shown to increase risk of reactivation (2, 16), whereas regimens involving hormonal therapy have not been shown to have an effect (2). More research is needed to determine which solid tumor chemotherapy regimens place patients at higher risk of HBV reactivation.

In conclusion, our case brings to light the need for definitive guidelines regarding HBV screening in patients receiving solid tumor chemotherapy. Since our patient did not have any symptoms of HBV infection or any risk factors associated with HBV infection, she would not have been identified through risk-adapted screening. We argue that universal screening should be considered prior to initiation of chemotherapy, not only for patients undergoing stem cell transplants and treatment with anti-CD20 agents, but also for patients receiving chemotherapy for solid tumor malignancies. HBV screening could help identify patients at risk for HBV reactivation and prevent complications of HBV reactivation through anti-viral prophylaxis. Although we advocate for universal screening, further research is needed to determine the most optimal strategy for HBV screening in patients receiving solid tumor chemotherapy, including examining the optimal HBV tests required for screening, financial burden, potential harm from overtreatment, and impact on patient morbidity and mortality.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this article.

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