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Deadly Trust in Anti-HBs: A Fatal Hepatitis B Reactivation

To the Editor:

Hepatitis B virus reactivation (HBVr) is a well-known complication for hepatitis B surface antigen (HBsAg)-positive patients undergoing immunosuppressive drug therapy. Consequently, guidelines from the European Association for the Study of the Liver (EASL)[1] and the American Association for the Study of Liver Diseases (AASLD) strongly recommend antiviral prophylaxis for these patients. But there is no consensus for HBsAg-negative patients, hepatitis B core antibody (anti-HBc)-positive patients, or hepatitis B surface antibody (anti-HBs)-positive patients undergoing immunosuppressive treatment. At present, the guidelines suggest the close monitoring of these individuals with HBV DNA for early detection of HBVr before elevated liver enzymes are detected and recommend offering on-demand rescue treatment with potent antiviral drugs.[1]

The early detection of HBVr after a patient starts chemotherapy is crucial but nearly impossible for many clinicians because slightly elevated liver enzymes are commonly assumed to be a hepatotoxic effect of chemotherapeutic agents, and the study of HBV DNA at each follow-up is a time-consuming procedure and is not cost effective.[2] In fact, published cases indicate that determination of HBVr is commonly delayed and identified through severely elevated liver enzymes.[3] Also, for HBsAg-negative patients receiving high-risk chemotherapy, not enough robust data is available regarding which modality (prophylaxis or on-demand treatment) is better than the other, whether the presence of anti-HBs in addition to anti-HBc provides any additional protection against HBVr, and whether using the anti-HBs status (titer) for early detection of HBVr is reliable.[1,4] Actually, HBVr is highly related to the type of chemotherapy in patients with previously resolved hepatitis B. One of the high-risk groups for HBVr is patients treated with B cell-depleting agents such as rituximab and ofatumumab that are monoclonal antibodies against the CD20 protein.[4] With the increasing use of monoclonal antibody-based chemotherapy in oncology, interest in sometimes-fatal HBVr in HBsAg-negative patients is increasing.[5] We present a case of fatal HBVr in a patient receiving rituximab chemotherapy that resulted from overconfidence in the protection of his anti-HBs-positive status.

A 61-year-old male diagnosed with accelerated chronic lymphocytic leukemia had no history of liver disease, drug abuse, or autoimmune diseases. The patient had a previously resolved hepatitis B infection (serology was HBsAg negative, anti-HBc positive, and anti-HBs positive, 38.13 IU/L titer and normal liver enzymes. Rituximab-based chemotherapy was started immediately with reliance on the patient's positive anti-HBs serology. After the patient's fourth chemotherapy, his hepatocellular liver enzymes increased 10-fold and his bilirubin level increased to 6 mg/dL. At that time, important changes were observed in his viral serology: he was anti-HBs negative and HBsAg positive, and his HBV DNA was 1×10^7 IU/mL. Tenofovir was started immediately, but clinical and laboratory improvement could not be obtained. Because the patient developed liver failure with hepatic encephalopathy and had elevated prothrombin time, he received a liver transplant, but he died 2 days after the transplant.

In recent years, fatal HBVr has been a problem among HBsAg-negative patients with previously resolved hepatitis B who are undergoing rituximab chemotherapy. Metaanalysis has shown that rituximab-based chemotherapy has a rate of HBVr more than 5-fold higher than nonrituximab chemotherapy in patients with previously resolved hepatitis B infection.[6] Nevertheless, many oncologists are not complying with the guidelines' recommendation for hepatitis B infection screening before instituting chemotherapy, and they do not have enough knowledge about hepatitis B serology and the outcomes of HBVr.[2,7] Positive anti-HBs does not provide protection against HBVr in patients receiving rituximab chemotherapy, probably because of the decrease in the antibody level resulting from the use of a B cell-depleting agent. Further, anti-HBs status is not a reliable marker for early detection of HBVr.[4] In previous published case series, more than half of the individuals died from fatal HBVr because of delayed diagnosis and treatment.[8-10]

To prevent potentially fatal HBVr in HBsAg-negative patients who are receiving rituximab chemotherapy, a group of Chinese authors recommended in 2009 the alternative approach of antiviral prophylaxis even though the EASL and AASLD guidelines recommend on-demand rescue treatment.[11] A guideline by the American Gastroenterological Association (AGA) published in 2015 strongly recommends antiviral prophylaxis for these high-risk patients.[4] We endorse the use of standard antiviral treatment in accordance with the AGA recommendation.

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Metabolically Healthy Obesity, Fitness, and Prognosis

To the Editor:

We read with interest the high-profile Research Letter by Bell and colleagues[1] from the Whitehall II study in a January 2015 issue of the *Journal of the American College of Cardiology,* suggesting that a high percentage of those who initially have metabolically healthy obesity develop metabolic abnormalities over time, more so than do lean patients. This suggestion has been heavily quoted in the medical and lay media, especially for such a short (800-word) Research Letter. Although this is a significant observation, major clinical events, cardiovascular disease, and all-cause mortality are much more important endpoints.

A very major limitation of this study and the Kramer et al[2] study that they reference, however, is that these studies were not fit vs fat studies, as these studies did not provide any information about cardiorespiratory fitness or aerobic exercise capacity—a critical predictor of prognosis. We discussed this point in detail in a recent *Journal of the American College of Cardiology* State of the Art on this topic[3] and in a recent published paper on metabolically healthy obesity[4] emphasizing the importance of cardiorespiratory fitness. Numerous papers have demonstrated that cardiorespiratory fitness is more important than adiposity in predicting long-term risk, and a 2014 metaanalysis of 10 studies[5] demonstrated that those who were overweight or obese but fit had half the long-term mortality as those who were lean and unfit and had similar survival compared with those who were lean and fit. Basically, these results demonstrate that if one is at least relatively fit (generally defined in some studies as not being in the bottom 20% and in other studies as not being in the bottom 33% of age- and gender-based cardiorespiratory fitness), body composition and adiposity essentially become nonrelevant: normal, overweight, or obese (at least mildly obese) persons who were fit all had a good prognosis. These data, however, may not apply to those with severe or morbid obesity who generally have a poor prognosis.[3]

We have demonstrated the same results in nearly 10,000 coronary heart disease patients[6] and in 2,066 heart failure patients,[7] showing that patients with coronary heart disease and heart failure who have good cardiorespiratory fitness have a favorable prognosis regardless of adiposity, which was reviewed in detail elsewhere.[3,4,6,7] Nevertheless, although metabolically healthy obesity may not be associated with increased coronary heart disease, it may be associated with an increase in heart failure,[8] but again, cardiorespiratory fitness is an important determinant.[3,4]

In a perfect world, everyone would be lean, fit, and metabolically healthy throughout adult life, but the most important factor for long-term prognosis is cardiorespiratory fitness—a much more important factor than fatness for determining long-term prognosis.[3-5] The major determinant of cardiorespiratory fitness is regular physical activity. The bottom line is that lean and fit people and overweight/obese and fit people stay healthy by maintaining high levels of physical activity.[3-7] Therefore, a major decrement in health (and metabolic health) is because of decrements in physical activity and, therefore, cardiorespiratory fitness. Whether lean or obese, being active maintains overall and metabolic health for both this and the next generation.[9]

Given the overwhelming and unequivocal nature of the results discussed above,[3-7,9] it is clear that changes in physical activity and cardiorespiratory fitness likely largely explain the results of Bell and colleagues.[1] Nevertheless, as with many epidemiologic studies,[1,2] data on these most important determinants of metabolic health and prognosis are lacking.

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