

A Forty-One Year Old Man Died of Hepatocellular Carcinoma from Hepatitis B

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A forty-one year old male American Chinese, born in China, college professor in good health except a history of hepatitis B carrier state for more than twenty years, presented to his primary care physician's office with intermittent epigastric discomfort over a two-months period, described as sharp pain, 6/10 at times, associated with nausea, bloating and flatulence. This was usually triggered after a heavy meal, would last several hours, relieved with bed rest or anti-acid agents. He has been doing well prior except described some occasional generalized fatigue. He denied any appetite changes or weight loss. He had been under a lot of stress at home and at work.

His past medical history is otherwise unremarkable except the carrier status for hepatitis B as described as above. He denies any history of sexually transmitted diseases. His last physician visit was 5 years ago. He is not on any medications except for occasional anti-acid for epigastric discomfort. He is married and lives with his wife and 1 month old baby son. He works as a researcher and professor. He is a non-smoker and an occasional alcoholic beverage drinker. He denies any drug use. His family history is negative for cancer, heart disease or diabetes.

Physical exam revealed a healthy appearing middle-aged man with stable vital signs. His height was 5'9" and weight was 177 lbs. His exam was unremarkable.

His laboratory test indicated normal liver function and blood counts. However, alpha fetoprotein was significantly elevated over 100. CT scan identified his liver to be 5cm with a hypervascular mass on the right lobe invading the aorta and the right kidney. There were also several surrounding enlarged lymph nodes, suggesting locally advanced hepatoma. CT scan of the chest and head as well as EGD and colonoscopy were all negative.

He was referred to the liver transplant surgeon and was considered not a surgical candidate. He was then referred to an Oncologist for further care. His condition progressively declined and he passed away five months later.

Discussion

Hepatocellular carcinoma (HCC) is a primary liver malignancy, the global incidence is about 15 cases per

incidence of HCC 137,000 new cases.¹ The most important risk factor is viral hepatitis, especially hepatitis B.²⁻³ Among Chinese population, 15-20% is described as HBV carriers (hepatitis B surface antigen positive). The relative risk of HCC among Hepatitis B carriers is 223 times that of non-carriers. These chronic carriers are usually not symptomatic and have normal liver function. Despite this, they are at risk of developing Hepatocellular carcinoma without signs of cirrhosis, active or advanced hepatitis. Unfortunately, the diagnosis is usually late⁴⁻⁵ and the prognosis is generally poor, as the case described above.

What should we learn from this case, and what are the preventive strategies, surveillance programs and current recommendations?

1. Hepatitis B screening

Who should be screened?⁶⁻⁷

Persons born in hyperendemic areas such as China; Men who have sex with men
Injection drug users;
Patients on dialysis;
HIV infected patients;
Pregnant women;
Family, household, and sexual contacts of HBV-infected persons;
Testing should include HBsAg and anti-HBs. Patients who are negative for these markers should be vaccinated.

2. Hepatitis B evaluation

Check coinfection with HCV and/or HIV; Testing for immunity to hepatitis A;
Laboratory tests: complete blood count, liver biochemical tests, tests for HBV replication (HBsAg, anti-HBe, HBV DNA); The viral load baseline level is correlated to cirrhosis incidence;
Screening for hepatocellular carcinoma with a right upper quadrant ultrasound and serum alpha fetoprotein;
Liver biopsy may be considered for patients:⁸⁻⁹

- 1) who meet criteria for chronic hepatitis (ie, HBsAg positive for > 6 months, serum HBV DNA > 10(5) copies/mL or >20,000 IU/mL, persistent or intermittent elevation in ALT/AST levels).
- 2) who do not meet current criteria for treatment but have serum HBV DNA 10(4) to 10(5) copies/mL (2000 to 20,000 IU/mL) and ALT/AST levels that are normal or mildly elevated (< 2x upper limit);
- 3) patients with histologically active or advanced liver disease may benefit from treatment.

3. Hepatitis B treatment - The goal is prevention of cirrhosis, HCC and death. Treatment options for chronic HBV include

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100,000 population per year, over 40 percent of all cases of HCC occur in mainland China, which has an annual

interferon (standard and pegylated), lamivudine, adefovir dipivoxil, telbivudine, entecavir and newly tenofovir.

- Interferon - Started 1990, was primarily recommended for treatment of young patients with well compensated liver disease. The advantage of interferon compared to the other options is its finite duration of treatment, the absence of selection of resistant mutants, and a more durable response. On the other hand, side effects from interferon are troubling for many patients, and can be severe. Furthermore, interferon cannot be used in patients with decompensated disease, plus interferon is quite costly.
- Lamivudine - It is the first oral agent on the market. The main advantages of lamivudine are its lower cost (approximate cost of \$7 per day) and their clinically proved safety, including its use during pregnancy (Category C). The main disadvantage of lamivudine is the high rate of drug resistance which largely limited its use with availability of other newer agents.¹⁰⁻¹¹
- Adefovir - The main advantage of adefovir is its activity against lamivudine-resistant HBV and a lower rate of drug resistance compared to lamivudine. However, virus suppression is slow at the approved dose and up to 25 percent of patients experience minimal or no viral suppression. The average price of adefovir is approximately \$15 to \$19 per day. Adefovir at high doses has been associated with nephrotoxicity.
- Entecavir - It is highly potent in its antiviral activity with a low rate of drug resistance. Entecavir has a more important role in primary treatment of HBV than in patients with lamivudine-resistant HBV. Entecavir offers good e antigen conversion rate. Entecavir may also have an important role in patients with decompensated cirrhosis because of its potent antiviral activity and low rate of drug resistance but its safety in this patient population has not been well studied. The disadvantage of this agent is its cost, about \$20 to \$25 per day.
- Telbivudine - Telbivudine appears to have slightly more potent antiviral effects compared with lamivudine and adefovir but it selects for the same resistant mutants as lamivudine and is more expensive (around \$16 per day). In addition, it is not safe for pregnancy (Category D). Thus, its role as primary therapy is limited.

Tenofovir disoproxil fumarate (TDF or PMPA), is used to treat HIV with new indication for HBV. Tenofovir seems more potent in suppressing HBV replication than Adefovir and appears to be equally effective against wild-type and lamivudine-resistant HBV. It is not only a potent agent, but also safe for pregnancy (Category B).

The HSV DNA should be monitored during therapy, not liver function tests. The optimal duration of therapy for the oral drugs is not well-established. Most patients receiving nucleoside/nucleotide analogue therapy will require at least four to five years of treatment, and some may require indefinite treatment.

4. Hepatocellular carcinoma screening

AASLD (12) guideline — Recommendations for surveillance for HCC have been issued by the American Association for

the Study of Liver Diseases (AASLD). The AASLD recommends surveillance for the following groups of Hepatitis B carriers:

1. Asian males ≥ 40
2. Asian females ≥ 50
3. All cirrhotic HBV carriers
4. Those with a family history of HCC
5. Africans over age 20

For patients not listed above, the risk varies depending upon the severity of the underlying liver disease, and current and past hepatic inflammatory activity. Patients with high HBV DNA concentrations and those with ongoing hepatic inflammation remain at risk for HCC as well as those who have hepatitis B cirrhosis.

The AASLD makes the following recommendations regarding surveillance:

1. Patients at high risk for developing HCC (described above) should be entered into surveillance programs.
2. Patients on the transplant waiting list should be screened for HCC.
3. Surveillance for HCC should be performed using ultrasonography.

Lastly, AFP alone should not be used for screening unless ultrasound is not available.

Patients should be screened at 6 to 12 month intervals. The surveillance interval does not need to be shortened for patients at higher risk of HCC.

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Editorial Comment

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Hepatitis B virus (HBV) infection is one of the major global public health problems. It is estimated that worldwide approximately 33% of people (~ 2 billion people) have been infected with HBV. Approximately 5% of the world's population (i.e., 350 million people) is chronically infected with HBV and 25% of them will develop serious consequences, such as chronic hepatitis B (CHB) with cirrhosis and hepatocellular carcinoma (HCC). Globally, the prevalence of HBV infection can be divided into high (i.e., 8%), intermediate (i.e., 2%–7%), and low (i.e., < 2%) endemic regions. It is well known that Southeast Asia, including mainland China and Taiwan, is one of the regions where prevalence of HBV infection is very high. Although HBV prevalence in the United States is considered low, growing incidence of this condition has been reported there, especially in Asian Americans, including Chinese Americans, because of improved public awareness and community screening.

From the case presented by Dr. Kong in this issue, we could further discuss the important role of primary care providers in preventing HBV infection, managing CHB and the related complications. First, we should always keep in mind on the high prevalence of HBV infection in Chinese Americans in our daily practice. The reported incidence of HBV infection varies from 6.1% to 14.8% in Asian Americans. It is recommended to screen for HBV infection in all immigrants from regions with high HBV prevalence, such as Southeast Asia. Recently, CDC has updated its recommendations for identification and public health management of persons with chronic hepatitis B virus infection.⁶ Thus, it is important to add HBV screen tests (HBsAg, anti-HBc total, and anti-HBs) to all Asian Americans who undergo the first routine medical checkup.

Secondly, we all know that HBV vaccination has been used for more than 2 decades. Many studies have demonstrated the safety and efficacy of HBV vaccinations. Large and long-term observations reported that universal application of HBV vaccination has resulted in reduced prevalence of new HBV infection and hepatocellular carcinoma (HCC) in Taiwan and mainland China. Universal HBV vaccination has also been recommended in this nation. Since the diagnosis of HBV infection is usually established by primary care providers, their role is critical in advising family screen,

providing HBV vaccination to the family members in need, counseling life style in reducing risk of HBV transmission. In addition, primary care providers should also work closely with our obstetric colleagues on reducing perinatal transmission of HBV from HBV-infected mothers to their newborns.

Thirdly, it is well known that HBV infection is associated with a significantly higher risk of HCC development. This could happen in the absence of cirrhosis. As we learnt from this case, regular followup and HCC screen are essential for Asian patients with chronic HBV infection. Thus, patient education on importance of regular medical followup should be provided at the time of HBV diagnosis. HCC screen can be carried out by serum alpha fetoprotein (AFP) and abdominal imaging, such as ultrasonography.

Fourthly, we should be aware that the significant advances have been made in the past decade in HBV treatment. Since lamivudine became the first oral agent for HBV in 1998, US FDA has approved five more HBV drugs, including four more nucleos(t)ide analogues (NAs) and peginterferon α -2a. These widely available HBV treatment regimens have made CHB a treatable disease. Although it remains to be improved, the updated recommendations of HBV treatment have been used to guide our practice in managing these diseases. Studies have indicated early HBV treatment will prevent disease progression and may decrease the risk of HCC development. It should be noted that HBV treatment with NAs may result in anti-viral resistance. Thus, when delivering HBV treatment, patient education, support, and followup are very important. Since HBV treatment sometimes can be complicated, the primary care providers may feel overwhelmed. Thus, it is recommended that the primary care providers may work closely with their GI/Hepatology colleagues in managing these patients.

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Squamous Cell Carcinoma of Lung Metastatic to a Mediastinal Lymph Node Involved by Chronic