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Screening for Hepatocellular Carcinoma (HCC) in a Hepatitis B Carrier

C K Tan, H S Ng

Mr Wong is a 38-year-old man who was discovered to be HBsAg positive when he tried to donate blood 20 years ago. He has been well throughout. Last month, his 48-year-old elder brother was diagnosed to have advanced liver cancer and is presently dying from liver failure. He was also HBsAg positive. Mr Wong now comes to see you because he is worried about getting liver cancer and suffering the same fate as his brother.

Question: What would you do?

Answer: Mr Wong is at risk of developing HCC because he is a hepatitis B carrier. His risk may be further increased because of a positive family history. He will not have any early warning symptoms when HCC develops and the only way to diagnose it at an early, potentially curable stage is to undergo regular screening.

You should do some tests to assess his hepatitis B status as well as to check if he has developed HCC.

Initial visit	Subsequent visits
HBsAg	AFP
HBeAg	ALT, AST
LFT	U/S liver
AFP	
U/S liver	

AFP : alphafetoprotein
U/S : utrasound

Mr Wong should also be advised to inform his other family members to be tested to see if they are also hepatitis B carriers.

His results came back as follows:

HBsAg positive
HBeAg positive
AFP 178 μg/L
(normal: 1 – 10)

LFT: total protein 78g/L (normal: 62 – 82)
albumin 43g/L (normal: 37 – 51)
bilirubin 14 μmol/L (normal:3 – 24)
SAP 95u/L (normal:32 – 103)
ALT 284u/L (normal: 7 – 36)
AST 178u/L (normal: 15 – 33)

U/S liver: Normal. No hepatic tumours seen.

Question: How do you interpret the results? What should be done next?

Answer: Mr Wong is still HBeAg positive and his ALT and AST are raised, indicating active hepatitis B replicative disease with ongoing necroinflammatory activity. His AFP is also elevated. AFP may be elevated in the absence of HCC, as in this case, when there is ongoing necroinflammatory activity in the liver.

As he is having active replicative hepatitis B disease, he should be referred to a specialist for further management.

Question: Mr Wong was referred to the Singapore General Hospital for assessment. The doctors there thought he was undergoing HBeAg to anti-HBe antibody seroconversion and therefore held back interferon treatment. After observation in SGH for a few months, his HBeAg became negative and ALT and AST were normalised. The AFP also normalised together with the resolution of necroinflammatory activity. His seroconversion was successful. Hence he was discharged back to you for follow-up.

Mr Wong: Doctor, I wish to be under surveillance by you for liver cancer. How is the screening done?

Answer: The screening involves blood tests as well as going for an ultrasound examination of the liver.

Alphafetoprotein (AFP) is a tumour marker associated with HCC. However, using AFP as a sole screening test for HCC is not ideal because of a low sensitivity of 64% at best and low positive predictive values of only 9% – 32%. The performance of ultrasound (U/S) as a surveillance tool is better, with sensitivity of 78% and positive predictive value of 73%. Thus screening programmes for HCC should combine both serum AFP estimation and ultrasound examination of the liver.

We usually also add on ALT and AST to the screening panel as a check on the necroinflammatory activity in the liver. As discussed above, this may be useful when trying to interpret an elevated AFP level.

Mr Wong: How often do I have to come for screening?

Answer: The screening is done every six months. Screening intervals reported in the literature range from 3 to 12 months. As expected, the shorter the screening interval, the higher is the rate of diagnosis of early HCC. However, this interval has to be cost-effective and thus should be based on the tumour doubling time. In a study from Taiwan by Sheu et al in 1985, the median tumour doubling time was found to be 117 days. The most rapidly growing hepatocellular carcinoma took 5 months to increase from an ultrasonically undetectable 1 cm to a

Department of Gastroenterology
Singapore General Hospital
Outram Road
Singapore 169608

C K Tan, MRCP (UK), FAMS
Consultant

H S Ng, M Med (Int Med), FRCP (Edin), FAMS
Senior Consultant and Head

Correspondence to:
Dr C K Tan

detectable 3 cm in size. Thus, 6-monthly screening intervals would allow detection of tumours previously not detected by ultrasound 6 months ago.

Question: So Mr Wong was started on the screening programme. His results were as follows:

LFT, AFP normal

U/S normal, no hepatic tumour

What do you tell Mr Wong?

Answer: Reassure him that he has no evidence of HCC presently. Also, his liver function is normal and his hepatitis B is quiescent. However, he will need to return in 6 months' time for blood tests and ultrasound examination of the liver.

Question: Mr Wong is a very compliant patient and has already been regularly seen for more than 2 years. He had just come for his routine screening last week and you have the following results:

AFP 50 μg/L (normal range 1 – 10 μg/L)

ALT, AST normal

U/S normal, no obvious hepatic tumour

What do you do?

Answer: The AFP is minimally elevated. As mentioned earlier, AFP can be elevated in the absence of HCC if there is necroinflammatory activity in the liver. The best example of this is when a patient is undergoing seroconversion from HBeAg positive to anti-HBe antibody positive. Here, Mr Wong's ALT and AST are normal and thus the mildly elevated AFP is not likely to be due to necroinflammation. Mr Wong should be reviewed earlier the next time round.

Question: So what do you tell Mr Wong?

Answer: Your liver tests this time show a very slight increase in the tumour marker. This may be non-specific as the ultrasound examination does not show any tumour. However, in view of this, you should come back earlier for blood tests again in 3 months' time.

Question: Mr Wong faithfully returns for repeat blood tests 3 months later. His results are as follows:

AFP 154 μg/L

ALT and AST normal

What do you do?

Answer: A rising AFP in the absence of necroinflammatory activity is ominous and may indicate the development of HCC. Mr Wong should be sent for a CT scan of the abdomen as it is more sensitive than U/S in detecting small lesions in the liver. However, we do not replace U/S with CT scan in routine screening as the latter is more expensive and subjects the patient to radiation. Alternatively, Mr Wong could be referred to the hospital or gastroenterologist for further assessment.

DISCUSSION

Hepatitis B carriers are certainly at increased risk of developing HCC. A landmark prospective study by Beasley et al showed an increased relative risk of 227 times that of the normal population[1]. Familial occurrence of HCC in hepatitis B carriers has also been well described, possibly due to genetic susceptibility, shared environmental factors or a particularly oncogenic strain of the virus[2,3]. Regular screening of hepatitis B carriers can discover early HCC where there is a higher chance of curative resection[4,5]. In a local study done in our department, a significantly higher proportion of HCC discovered on screening were operable, compared to those who presented late with symptoms of HCC (49% vs 8% respectively).

Patients at risk of developing HCC can benefit from regular screening. The increased risk of developing HCC and the absence of symptoms in early HCC must be explained and stressed to the patients if we expect them to return regularly every 6 months when they are feeling perfectly well.

The cornerstones of HCC screening are the serum AFP measurement and ultrasound examination of the liver. Either of them may detect early HCC, at a stage where curative surgery is feasible. We must constantly heighten our awareness to possible HCC when running a screening programme. It is mandatory to exclude HCC if there is a persistently elevated or rising AFP even if the U/S is normal or if there is a suspicious U/S even in the face of a normal AFP.

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