Clathrin heavy chain (CHC) staining for the diagnosis of small hepatocellular carcinoma(◆)

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Article commented:

Di Tommaso L, Destro A, Fabbris V, Spagnuolo G, Laura Fracanzani A, Fargion S, et al. Diagnostic accuracy of clathrin heavy chain staining in a marker panel for the diagnosis of small hepatocellular carcinoma. Hepatology 2011; 53: 1549-57.

Original abstract

The American Association for the Study of Liver Diseases guidelines recommend the use of all available markers for improving the accuracy of the diagnosis of small hepatocellular carcinoma (HCC). To determine whether clathrin heavy chain (CHC), a novel HCC marker, is effective in combination with glypican 3 (GPC3), heat shock protein 70, and glutamine synthetase, we compared the performances of a three-marker panel (without CHC) and a four-marker panel (with CHC) in a series of small HCCs (≤ 2 cm) and nonsmall HCCs by core biopsy with a 20- to 21-gauge needle. The series included 39 nonsmall HCCs and 47 small HCCs (86 in all); the latter showed a well-differentiated histology [small grade 1 (G1)] in 30 cases (63.8%). The panel specificity was analyzed with the adjacent/extranodular cirrhotic liver (n = 30) and low-grade (n = 15) and high-grade dysplastic nodules (n = 16) as a control group. Absolute specificity (100%) for HCC was obtained only when at least two of the markers were positive (which two markers were positive did not matter). The addition of CHC to the panel increased the diagnostic accuracy for small HCCs (from 76.9 to 84.3%), and there was an important gain in sensitivity (from 46.8 to 63.8%). The four-marker panel had lower rates of accuracy (67.4%) and sensitivity (50%) for small G1 HCCs vs. nonsmall G1 HCCs (93.9 and 88.2%, respectively). In seven cases (including six small G1 HCCs), there was no staining with any of the markers. Cirrhotic control livers were stained for CHC in four cases (13.3%) and for GPC3 in one case (3.3%). **Conclusion.** The addition of CHC to the panel supports the diagnosis of small HCCs in challenging nodules on thin core biopsy samples. Small G1 HCCs include a group of earlier tumors characterized by a more silent phenotype and the progressive acquisition of the markers under study. The search for additional markers for early HCC diagnosis is warranted.

Comment

Hepatocellular carcinoma (HCC), the most frequent type of primary liver cancer, is the fifth most common solid tumor and the third most common cause of cancer mortality.[1] The American Association for the Study of Liver Diseases (AASLD) guidelines[1] suggest that the diagnosis of HCC can be made without a tissue biopsy in patients with chronic liver disease and cirrhosis who have a mass between 1-2 cm in size if a mass shows characteristic radiologic features on at least two dynamic imaging techniques. Lesions showing typical features by both imaging techniques should be treated as HCC.[2] However, if the results of the two techniques are discordant or if both techniques give atypical results, then a tissue biopsy is required to confirm the diagnosis. If the lesion is larger than 2 cm, only a single dynamic imaging study is necessary to confirm the diagnosis if the findings are typical of HCC. If the findings are not typical, a biopsy should be performed. This recommendation has been supported by a prospective validation.[3]

In addition to morphological examination an immunohistochemistry (IHC) panel of three markers

of malignant transformation [Glypican-3 (GPC3), heat shock protein 70 (HSP70) and glutamine synthetase (GS)] has been endorsed by the AASLD[2] to aid in the detection of malignancy in both surgical and liver biopsy specimens.[4,5] The presence of any two positive IHC markers of malignant transformation displayed a sensitivity of 72% and a specificity of 100% for detecting malignancies in surgical specimens.[4] In contrast the presence of two positive IHC marker of malignant transformation displayed a sensitivity of 50% in liver biopsies with a specificity of 100%.[5]

The present article attempts to improve the sensitivity levels of the above mentioned 3-panel IHC approach for the diagnosis of small HCC in liver biopsies, by the addition of clathrin heavy chain (CHC). CHC, an endothelial marker, appears to be overexpressed in HCC and has already shown promising results in surgical specimens, especially in combination with GPC3.[6]

A total of 86 HCCs were evaluated: forty seven small HCCs (< 2 cm) and 39 non-small HCCs (> 2 cm). The authors state that the diagnosis of the 86 cases was conducted based on morphologic features obtained by examination of H&E sections. However, no morphologic criteria to distinguish low-grade dysplastic from high-grade dysplastic nodules and HCC are provided. Given the difficulty of distinguishing low grade dysplastic nodules from well differentiated HCC in liver biopsies on morphological grounds, failure to include such criteria raises the question on whether the authors consider dysplastic nodules small HCCs.

CHC staining was absent in non-malignant lesions, but if positive with another marker of the 3-panel IHC system appeared to increase the sensitivity to detect small HCC lesions by 17%. The accuracy of diagnosis however, was still only within the 70 to 80% range, in contrast to a 100% accurate diagnosis obtained on H&E examination in this study set. Furthermore, the authors observed a diagnostic accuracy of 73% when four markers were positive, and 90% when only one marker was used in the non small HCC lesions - this is difficult to understand.

While the addition of CHC may improve the sensitivity in certain lesions it is doubtful from a practical perspective whether this observation warrants an introduction of CHC into the currently recommended IHC-panel.

Aside from the challenges associated with validating and maintaining accurate IHC results, we feel very strongly that IHC can only function as an adjunct to clinical, radiological and morphological observations for the diagnosis of small HCC, especially in the setting of liver biopsies.

REFERENCES

1. Bruix J, Sherman M. Practice Guidelines Committee, AASLD. Management of hepatocellular carcinoma. *Hepatology* 2005; 42: 1208-36.
2. Iannaccone R, Laghi A, Catalano C, et al. Hepatocellular carcinoma: role of unenhanced and delayed phase multidetector row helical CT in patients with cirrhosis. *Radiology* 2005; 234: 460-7.
3. Forner A, Vilana R, Ayuso C, Bianchi L, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008; 47: 97-104.
4. Di Tommaso L, Franchi G, Park YN et al. Diagnostic value of HSP70, glypican 3, and glutamine synthetase in heaptocellular nodules in cirrhosis. *Hepatology* 2007; 45: 725-34.
5. Di Tommaso L, Destro A, Seok JY, et al. The application of the markers (HSP70, PPC3 and GS) in liver biopsies is useful for the detection of hepatocellular carcinoma. *J Hepatol* 2009; 50: 746-54.
6. Seimiya M, Tomonaga T, Matsushita K, Sunaga M, et al. Identification of novel immunohistochemical tumor markers for primary hepatocellular carcinoma; clathrin heavy chain and formi-minotransferase cyclodeaminase. *Hepatology* 2008; 48: 519-30.