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Immunohistochemical approach to hepatocellular carcinoma (HCC)

Aušrinė Barakauskienė[1, 2],

Miglė Šumkauskaitė[2]

[1] *National Centre of Pathology, Vilnius, Lithuania*

[2] *Faculty of Medicine, Vilnius University, Lithuania*

Background. The distinction of hepatocellular carcinoma (HCC) from other neoplasms requires the use of immunohistochemistry. There are many usable markers, but not all of them are equally beneficial, and there is no unique antibodies panel. The aim of the study was to outline an immunohistochemical approach for the HCC diagnosis, as well as to recommend using synoptic report in routine practice.

Materials and methods. Formalin-fixed and paraffin-embedded tissue samples of 192 patients with documented hepatic neoplasm were collected from the National Centre of Pathology in Vilnius during 2003–2007. 64 samples with documented HCC, 11 metastatic adenocarcinomas (MA) and 20 benign neoplasms (BN) were selected for the study, for which immunostaining was performed with HepPar1, CD10, CD31, CD34, CK7, CK8 and CK20.

Results. HepPar1 was positive in all tumour grades; the sensitivity was 96.6%, and the specificity was 100%. CD10 stained 40/50 HCC; the sensitivity was 80%, and the specificity, 50%. CD10 was less specific compared with HepPar1 ($p < 0.002$); in cases of well-differentiated tumours immunoreactivity was seen more rarely ($p < 0.01$). The sensitivity of CD34 was 100%, and the specificity amounted to 97.1%. CD34 was the most sensitive compared with other markers ($p < 0.05$). CD31 and cytokeratins immunoreactivity was seen in all types of tumours.

Conclusions. The combination of HepPar1, CD10 and CD34 confirms the diagnosis of HCC in most cases. HepPar1 is the most reliable marker for HCC differentiation. CD34 promises the diagnosis of HCC and distinguishes it from benign processes such as hepatic adenoma and focal nodular hyperplasia.

Key words: hepatocellular adenoma (HCA), focal nodular hyperplasia (FNH), hepatocellular carcinoma (HCC), immunohistochemistry (IH)

INTRODUCTION

HCC is the most common primary hepatic malignancy of adults. It is a primary malignant neoplasm composed of cells that differentiate in some way in the manner of hepatocytes (1). Since the cells of HCC mimic normal liver cells, they may produce any of cellular products that can be found in hepatocytes, both in health and in disease, and, if present, these are readily demonstrated by immunostaining (2). Many of these can also be found in tumours other than HCC, and so are of little use in differential diagnosis (3). It is sometimes difficult to consistently distinguish well-differentiated HCC from benign lesions, such as hepatocellular adenoma or dysplastic nodules and, similarly, distinguish poorly differentiated HCC from poorly differentiated cholangiocarcinoma or metastatic adenocarcinoma. However, selected immunostains, taken in the context of other morphological features, can be very helpful in establishing the diagnosis of HCC in difficult cases (1, 4). It is nevertheless true that immunohistochemistry plays a crucial role in the diagnosis of hepatocellular carcinoma and in its distinction from other primary and metastatic neoplasms nowadays. Because limited tissue is available with core biopsies, appropriate selection of antibodies is imperative (5).

The aim of the article is to review cost-effective antibodies used for the diagnosis of HCC and to outline an immunohistochemical approach based on our data (National Centre of Pathology in Vilnius during 2003–2007). It is very important for the clinicians to get maximum information about the liver tumour in the final report. The standardization of the pathological diagnosis could be implicated in the synoptic report of liver focal lesions as it is suggested in other centres according tissue reporting recommendations. Therefore, we are suggesting using hepatic tumour features which could be included in the final report as a synoptic checklist (6, 7) to make this procedure more standardized.

MATERIALS AND METHODS

Formalin-fixed and paraffin-embedded tissue samples of 192 patients with documented hepatic neoplasm (95 cases with HCC, 61 with MA, and 36 with BN) were collected from the National Centre of Pathology in Vilnius during 2003–2007.

Correspondence to: Dr. Aušrinė Barakauskienė, National Centre of Pathology, P. Baublio 5, LT-08406 Vilnius, Lithuania.
E-mail: ausrine.barakauskiene@vpc.lt

For further analysis we selected the samples only where immunostaining was performed: 64 cases with documented HCC, 11 with MA and 20 with BN: 6 hepatic haemangiomas, 5 hepatocellular adenomas, 4 focal nodular hyperplasias, 2 biliary microhamartomas, 1 benign dysplastic nodule, 1 hepatobiliary cyst adenoma, 1 case with macro regenerative nodule. All the analysed cases consisted of 62 biopsy specimens (65.3%) and 33 surgical specimens (34.7%), while 47 biopsy specimens (73.4%) and 17 surgical specimen (26.6%) accounted for all HCC cases. Hospital records were used to verify age, sex.

HCC grading was performed using the criteria of Edmundson and Steiner. This grading system is based on cytological and architectural disturbances, which are expressed in four grades. The most usual types of histological grade of HCC are I and II, while III and IV are less frequent. Criteria simplified to a 3-grade system in which, essentially, grades I and II become grade I, grade III becomes grade II, while grade IV becomes grade III are used in some institutions (6, 7).

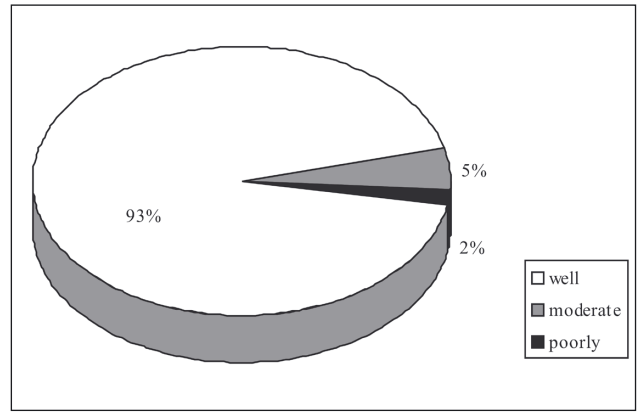
HepPar1 (Monoclonal Mouse Anti-Human Hepatocyte, code No. M 7158, 1 : 1500, DakoCytomation, the antibody labels the hepatocytes), CD10 (Mouse Monoclonal Antibody, code No. NCL-CD10-270, clone 56C6, 1 : 50, DakoCytomation, the antibody labels bile canaliculi), CD31 (Monoclonal Mouse Anti-Human CD31, code No. M0823, clone JC70A, 1 : 50, DakoCytomation, the antibody labels endothelial cells), CD34 (Monoclonal Mouse Anti-Human CD34 Class II, code No. M 7165, clone QBEnd-10, 1 : 100, DakoCytomation, the antibody labels endothelial cells), CK7 (Monoclonal Mouse Anti-Human Cytokeratin 7, code No. M 7018, clone OV-TL 12/30, 1 : 400, DakoCytomation, the antibody labels biliary and pancreatic ducts), CK8 (Monoclonal Mouse Anti-Human Cytokeratin 8, LMW code No. M 7018, clone 35ßH11, 1 : 100, DakoCytomation, the antibody labels nonsquamous epithelium) and CK20 (Monoclonal Antibody to Human Cytokeratin 20, clone Ks20.8, 1 : 30, DakoCytomation, the antibody binds to intestinal and gastric foveolar epithelium, urothelial umbrella cells, adenocarcinomas of the colon, transitional cell carcinomas, merkel cell tumors of the skin) were used to differentiate the tumour. Expressions of markers were compared with HCC grade and lesion type.

All statistical tests were performed with the Program Statistical Package for the Social Sciences (SPSS version 12.0 for Windows). The t-test was used to determine the statistical significance of differences. Probability (p) values of less than 0.05 were considered statistically significant. The sensitivity and specificity of immunostaining were calculated using SnNouts and SpPins test.

RESULTS

The mean ±SD age of patients with HCC was 61.42 ± 12.60 years. Male to female ratio was 7 (56 males and 8 females) and mean ±SD age of patients in each sex was 60.66 ± 13.10 years and 66.75 ± 11.27 years, respectively. The mean ±SD age of patients with MA diagnosis was 63.18 ± 10.53 years. Male to female ratio was 0.2 (2 males and 9 females). In patients group with BN the mean ±SD age was 56.55 ± 14.75 years. Male to female ratio was 0.25 (4 males and 16 females).

Immunostaining was performed (Pie chart) for 64 cases with documented HCC. HCC was graded as well as differentiated in 60 cases, moderately differentiated in 3, and poorly differentiated in 1.



Pie chart. HCC differentiation (using the criteria of Edmundson and Steiner) (%)

There were 3 (4.7%) lesion types of fibrolamellar type of HCC founded; the other 61 (95.3%) were conventional HCC. In the background of HCC there was cirrhosis in 47 (73.4%) samples. Cirrhosis in BN patients was detected in 2 (10.0%) cases. The results of all immunohistochemical staining are summarized in Table 1.

HepPar1 was positive in more than 96% HCC cases and was negative in MA and BN ($p < 0.0001$). HepPar1 was positive in all tumour grades (Edmondson and Steiner grading system): I grade – 52/54 (96.3%), II – 3 (100%), III – 1 (100%) and in all lesion types. The sensitivity of HepPar1 for HCC was 96.6%, and the specificity was 100%.

CD10 stained 40 of 50 HCC, it was negative for MA (0/1) and positive for BN (1/1). Immunoreactivity was seen in 38/46 cases of well-differentiated HCC, 1/3 – moderately differentiated HCC and 1/1 – poorly differentiated HCC. The sensitivity of CD10 for HCC was 80%, and the specificity was 50%. CD10 was less specific for HCC compared with HepPar1 ($p < 0.002$); in cases of well-differentiated tumours CD10 immunoreactivity was seen more rarely ($p < 0.01$).

CD34 was positive in all HCC cases (54/54), was negative with all MA cases and was to 5% (1/19) positive with BN, in dysplastic nodule. CD34 was the most sensitive for HCC in comparison with other markers ($p < 0.05$). The sensitivity of CD34 for HCC was 100%, and the specificity was 97.1%.

Table 1. **Immunohistochemical staining in hepatic neoplasms**

Neoplasm	HepPar1	CD 10	CD 34	CK 7	CK 8	CK 20
HCC	56 (96.6%)	40 (80.0%)	54 (100%)	5 (25.0%)	38 (100%)	1 (10.0%)
MA	0	0	0	4 (100%)	1 (100%)	0
BN	0	1(100%)	1(5.3%)	3 (100%)	1 (100%)	0

CD31 immunoreactivity was positive in all types of tumours and benign lesions. The sensitivity of CD31 for HCC was 100%, and the specificity was 0%.

CK7 stained 5 of 20 HCC, was positive with all MA (4/4) and BN (3/3) cases. The sensitivity of CK7 for HCC was 25%, and the specificity was 0%. CK8 was positive with all cases of HCC, MA and BN. Consequently the sensitivity of CK8 for HCC was 100%, and the specificity was 0%. CK20 stained 1 of 10 HCC and was negative for MA (0/1) and BN (0/0). The sensitivity of CK20 for HCC was 10%, and the specificity was 100%. No difference was seen between cytokeratins immunoreactivity in HCC, MA and BN cases ($p > 0.05$), except CK7, which in MA cases was more often positive compared with HCC ($p < 0.04$).

DISCUSSION

There are many usable immunohistochemical markers, but not all of them are equally beneficial, and there is no unique antibodies panel for HCC diagnosis. The aim of all pathology laboratories is to find such a panel based on their own practice. We tried to find the immunohistochemical approach for the correct HCC diagnosis based on literature and confirmed by our own data from routine pathology practice with the well known cost-effective antibodies which could be used not only for HCC diagnosis but also for other lesions with success.

HepPar1 (also known as hepatocyte antigen) is a monoclonal antibody specifically developed to react with hepatocytes in a diffuse cytoplasmic granular staining pattern in normal and neoplastic hepatocytes (Fig. 1). It rarely reacts with bile duct and nonparenchymal liver cells (8, 9). The results of other studies demonstrate that HepPar1 is the most sensitive and specific immunohistochemical marker. Because it is positive in normal liver and adenomas, it is not useful for distinction of benign *versus* malignant hepatocellular lesions (10, 11). HepPar1 was positive in all tumour grades using Edmondson and Steiner grading system. The sensitivity of HepPar1 for HCC was 96.6%, and the specificity was 100% in our study proving the usefulness of this monoclonal antibody in differential diagnosis of primary malignancy in the liver. It is known that in addition, HepPar1 is extremely helpful in limited tissue samples from fine needle aspiration FNA (2, 8, 11), but this practice is no longer used in our Institute. When compared with immunohistochemistry of hepatocyte antigen and glypican-3 (GPC3), the latter was shown to be significantly much more specific and sensitive for hepatocellular carcinomas and now is attracting attention for the promise both as marker of hepatocellular carcinoma in routine histological examination and as target in monoclonal antibody-based hepatocellular carcinoma therapy (5).

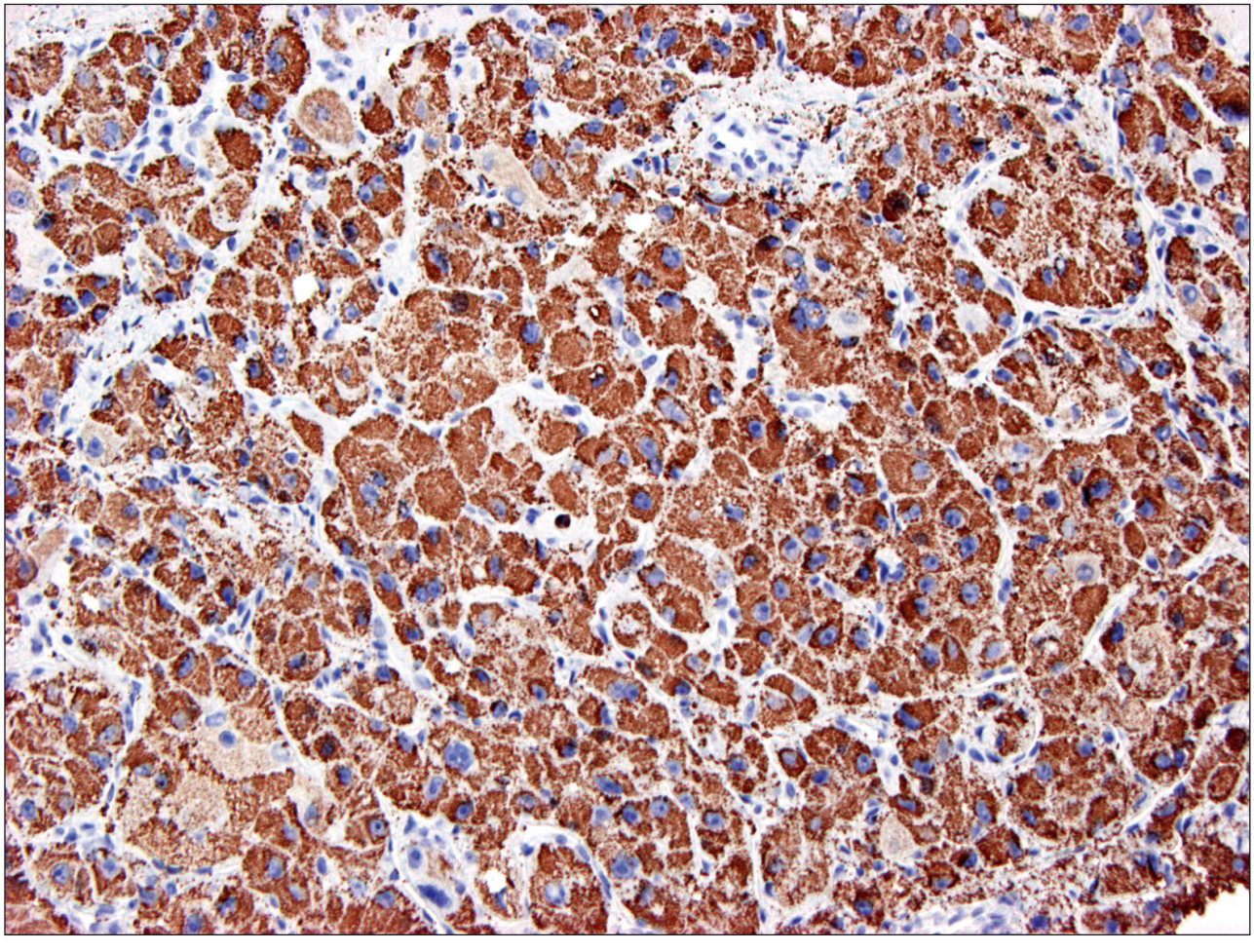


Fig. 1. HepPar1 (monoclonal antibody) specifically reacts with hepatocytes in a diffuse cytoplasmic granular staining pattern in neoplastic hepatocytes (×200)

As with all the antibodies, the pitfalls of the use of HepPar1 antibody should be known.

Pitfalls in Diagnosis

HepPar1 is more likely to be negative and less sensitive in poorly differentiated and sclerosing HCC. Patchy staining is seen in about 20% of HCC's and hence needle biopsies can be negative. Although most adenocarcinomas are negative, oesophageal, lung adenocarcinomas, rare carcinomas with hepatoid morphology in the gastrointestinal tract and pancreas can occasionally show strong positive reactions, therefore, predictive value of positive HepPar1 by itself is not high in making this distinction and should be used together with other antibodies.

Expression of CD10 in non-neoplastic and neoplastic hepatocytes appears to correlate inversely with their state of proliferation or differentiation (12). CD10 staining has a canalicular pattern similar to polyclonal CEA and vilin in HCC (Fig. 2) (4, 13). Recent studies demonstrate that canalicular staining for CD10 appears to be a highly specific marker for hepatocytic differentiation (14). CD10 appears to be a useful marker in discriminating between HCC and metastatic, but does not provide discrimination between HCC and benign hepatocytes (15). The sensitivity of CD10 for HCC in our study was 80%, and the specificity was 50%. The other studies founded CD 10 positivity only in 61% of HCC (16).

Pitfalls in Diagnosis

Even though the canalicular pattern is not seen in adenocarcinoma, CD10 is a poor substitute because of low sensitivity (50% for CD10) and could not be used for the diagnostic purposes alone.

It is interesting to note that the expression of endothelial cell markers CD31, CD34 in the vascular tree is heterogeneous with a specific pattern for individual vessel types and different anatomic compartments of the same organ. Sinusoids of the liver are diffusely positive for CD31 and negative for CD34 and only express CD34 in the periportal or periseptal area in the liver (17, 18). This type of staining was proven in all cases with cirrhotic background of HCC of our study. The sinusoid-like vasculature in HCC often shows strong expression of CD34 (Fig. 3), which is attributed to the capillarization of sinusoids leading to a change in the phenotype of endothelial cells (19–22). The sinusoidal pattern observed in CD34 positivity is a unique feature of HCC among carcinomas and has high specificity, as this pattern is not observed in adenocarcinoma. In our study CD34 was the most sensitive for HCC in comparison with other markers ($p < 0.05$). However, other authors have found low sensitivity (~20%–40%) and because better antibodies are available, CD34 is not routinely used for this distinction in other centres. We are using this antibody for differential diagnosis for many other suspected malignancies, thus, to use it for HCC as well is important for our Centre. The data of our study shows that CD34 can be helpful

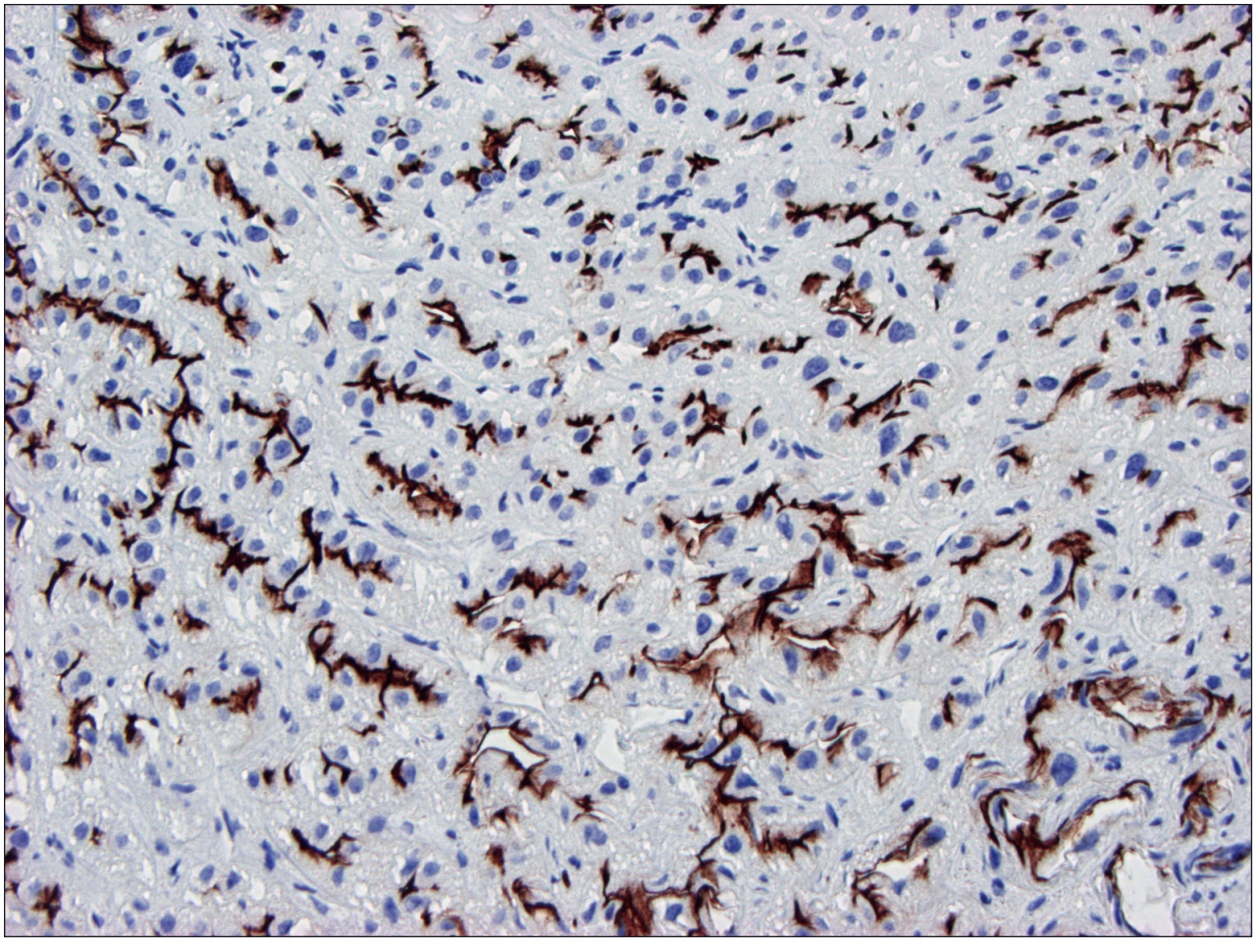


Fig. 2. CD10 staining shows a canalicular pattern similar in HCC (×200)

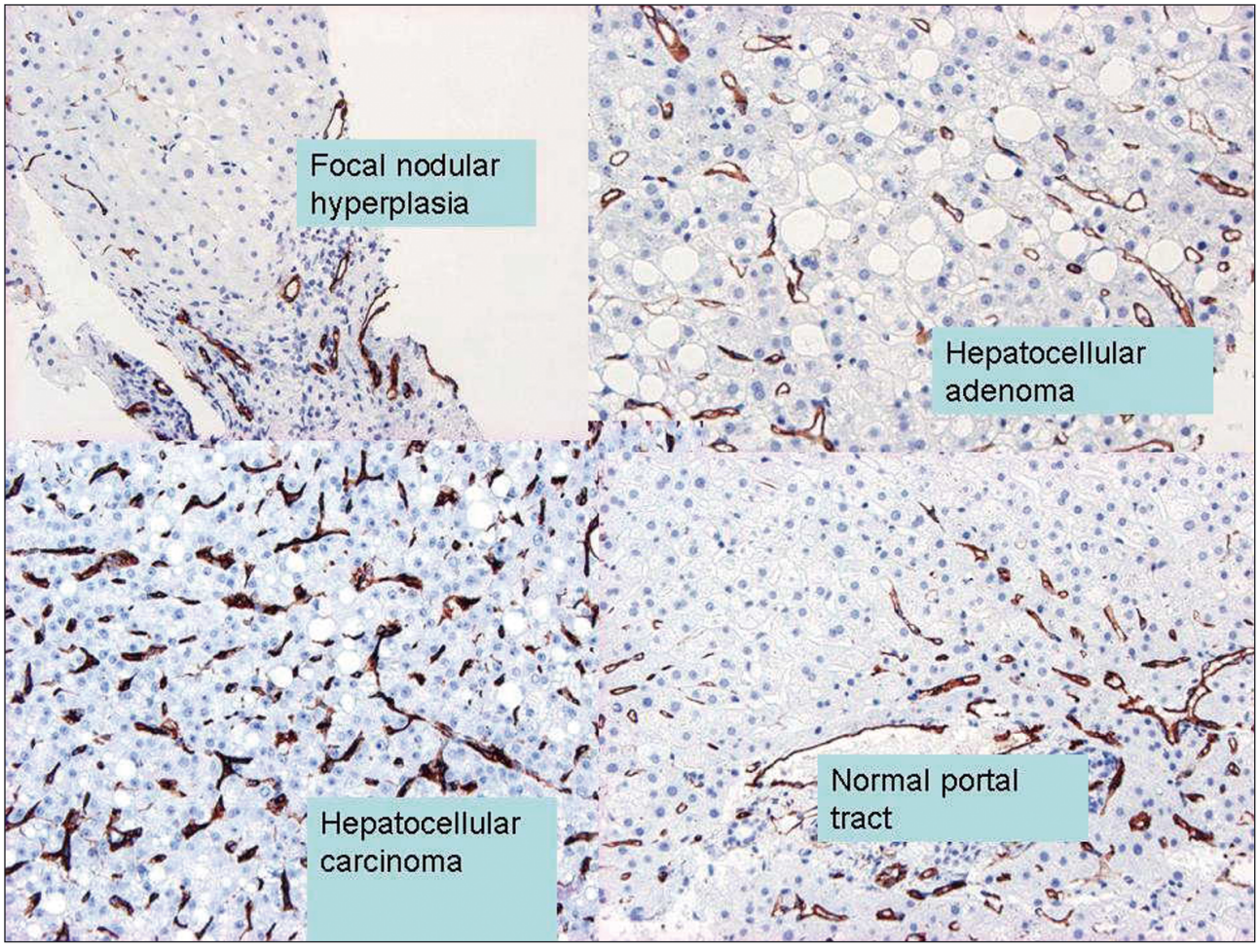


Fig. 3. The sinusoid-like vasculature in HCC shows strong continuous expression of CD34 different from benign lesions (×200)

in the distinction of a well-differentiated hepatic neoplasm from normal or cirrhotic liver, especially in small biopsy specimens (23). Some authors say that CD34 is not useful in the distinction between benign and malignant hepatocellular lesions as similar CD34 staining can be seen in focal nodular hyperplasia and hepatic adenomas (24). We think that 'similar' CD34 staining could be treated differently between the pathologists: in benign lesions as hepatocellular adenoma we found CD34 staining to be weak and discontinuous in comparison with continuous and strong sinusoid reaction in HCC cases. In focal nodular hyperplasia we found the weak positive staining only in peripheral arias and not in the middle of the lesion. Therefore this sinusoidal pattern observed in CD34 positivity as a unique feature of HCC among carcinomas could be included in HCC IH algorithm but only together with other markers. There is a different story with the other endothelial antibody, CD31. Because sinusoids of the normal liver and benign or malignant liver lesions are diffusely positive for CD31 this antibody could not discriminate the liver lesions. CD31 immunoreactivity was positive in all types of tumours in our study.

Cytokeratins

Normal and neoplastic (benign and malignant) hepatocytes express cytokeratin (CK) 8 and CK18 and are generally negative for CK7, CK19, and CK20 (3, 5). The majority of HCC's are negative for CK7 and CK20. Nearly 75% of HCC's are $CK7^{-}/CK20^{-}$, 20% are $CK7^{+}/CK20^{-}$, and 5% are $CK7^{+}/CK20^{+}$. The commonly used keratin antibodies (AE1/AE3, CAM 5.2, CK7, and CK20) can be expressed in both HCC and adenocarcinoma, limiting their value in this differential diagnosis (5, 25). No difference was seen between cytokeratins immunoreactivity in HCC, MA and BN cases ($p > 0.05$), except CK7, which in MA cases was more often positive compared with HCC ($p < 0.04$). So in conclusion cytokeratins have limiting value in differential diagnosis of HCC and their use is not important to verify hepatocellular carcinoma as carcinoma itself but should be used to exclude the metastasis of other primary tumours.

Albumin could be used *in situ* hybridization in the diagnosis of HCC. This antibody is specific for hepatocellular differentiation and has high sensitivity (90%). The combination of albumin *in situ* hybridization and HepPar1 can yield 100% sensitivity for diagnosis of HCC. However; the use of this test is limited by its restricted availability and is not used in our Centre.

Synoptic report

We found it practical and useful to simplify HCC grading system in synoptic report as it has been done in some institutions. We recommend using the synoptic report in routine practice. It is generated from published studies on the diagnostic features and

prognosis for primary and metastatic epithelial tumours in the liver (6, 7).

CONCLUSIONS

The combination of HepPar1, CD10 and CD34 confirms the diagnosis of HCC in most cases and will guide the selection of immunohistochemical markers for further workup.

HepPar1 is the most reliable marker for HCC differentiation in limited tissue samples from core biopsies.

CD34 promises the diagnosis of HCC and distinguishes it from benign processes such as hepatic adenoma and focal nodular hyperplasia.

CD10 comparing with HepPar1 is less specific for HCC, but it is a sensitive antigen.

CD31 is not a reliable marker to discriminate tumour neovascularization. Cytokeratins have limited value in differential diagnosis of HCC. Consequently, usage of CD31 and cytokeratins for confirming HCC diagnosis is unreliable and economically inexpedient.

Simplified criteria of Edmondson and Steiner could be used in routine practice in HCC grading and could be implicated in HCC synoptic report.

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References

1. Burt AD, Portmann BC, Ferrell LD. MacSween's Pathology of the Liver. 5th ed. 2007; 771–87.
2. Lamps LW, Folpe AL. The diagnostic value of hepatocyte paraffin antibody 1 in differentiating hepatocellular neoplasms from nonhepatic tumors: a review. Adv Anat Pathol 2003; 10: 39–43.
3. Johnson DE, Herndier BG, Medeiros LJ, Warnke RA, Rouse RV. The diagnostic utility of the keratin profiles of hepatocellular carcinoma and cholangiocarcinoma. Am J Surg Pathol 1988; 12(3): 187–97.
4. Lau SK, Prakash S, Geller SA et al. Comparative immunohistochemical profile of hepatocellular carcinoma, cholangiocarcinoma, and metastatic adenocarcinoma. Hum Pathol 2002; 33: 1175–81.
5. Kakar S, Gown AM, Goodman ZD, Ferrell LD. Best practices in diagnostic immunohistochemistry: hepatocellular carcinoma versus metastatic neoplasms. Arch Pathol Lab Med 2007; 131(11): 1648–54.
6. The Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of tissues removed as part of the surgical treatment of malignant liver tumors. Am J Clin Pathol 2005; 123: 494–8.
7. Craig JR, Marchevsky AM. Protocol applies to hepatocellular carcinoma and cholangiocarcinoma. College of American Pathologists 2005; 4–15.
8. Siddiqui MT, Saboorian MH, Gokaslan ST, Ashfaq R. Diagnostic utility of the HepPar1 antibody to differentiate hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration samples. Cancer 2002; 96(1): 49–52.
9. Wennerberg AE, Nalesnik MA, Coleman WB. Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. Am J Pathol 1993; 143: 1050–4.
10. Chu PG, Ishizawa S, Wu E, Weiss LM. Hepatocyte antigen as a marker of hepatocellular carcinoma: an immunohistochemical comparison to carcinoembryonic antigen, CD10, and alpha-fetoprotein. Am J Surg Pathol 2002; 26(8): 978–88.
11. Fan Z, van de Rijn M, Montgomery K, Rouse RV. Hep par 1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumors tested using tissue microarrays and conventional tissue sections. Mod Pathol 2003; 16(2): 137–44.
12. Röcken C, Carl-McGrath S, Gräntzdörffer I, Mantke R, Roessner A, Lendeckel U. Ectopeptidases are differentially expressed in hepatocellular carcinomas. Int J Oncol 2004; 24(3): 487–95.
13. Morrison C, Marsh W Jr, Frankel WL. A comparison of CD10 to pCEA, MOC-31 and hepatocyte for the distinction of malignant tumors in the liver. Mod Pathol 2002; 15: 1279–87.
14. Borscheri N, Roessner A, Röcken C. Canalicular immunostaining of neprilysin (CD10) as a diagnostic marker for hepatocellular carcinomas. The Am J Surg Pathol 2001; 25(10): 1297–303.
15. Lin F, Abdallah H, Meschter S. Diagnostic utility of CD10 in differentiating hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration biopsy (FNAB) of the liver. Diagn Cytopathol 2004; 30(2): 92–7.
16. Standards and Datasets for Reporting Cancers. Dataset for liver resection specimens and liver biopsies for primary and metastatic carcinoma. London: The Royal College of Pathologists; 2007: 21–2.
17. Pusztaszeri MP, Seelentag W, Bosman FT. Immunohistochemical expression of endothelial markers CD31, CD34, von Willebrand factor, and Fli-1 in normal human tissues. J Histochem Cytochem 2006; 54(4): 385–95.
18. De Boer WB, Segal A, Frost FA, Sterrett GF. Can CD34 discriminate between benign and malignant hepatocytic lesions in fine-needle aspirates and thin core biopsies? Cancer 2000; 90(5): 273–8.
19. Heukamp LC, Fischer HP, Schirmacher P, Chen X, Breuhahn K, Nicolay C, Büttner R, Gütgemann I. Podocalyxin-like protein 1 expression in primary hepatic tumours and tumour-like lesions. Histopathology 2006; 49(3): 242–7.
20. Saad RS, Luckasevic TM, Noga CM, Johnson DR, Silverman JF, Liu YL. Diagnostic value of HepPar1, pCEA, CD10, and CD34 expression in separating hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration cytology. Diagn Cytopathol 2004; 30(1): 1–6.
21. Nagy P, László V, Schaff Z. A hepatokarcinogenezis folyamata humán májban. Magyar onkologia 2006; 50(2): 107–13.
22. Frachon S, Gouysse G, Dumortier J et al. Endothelial cell marker expression in dysplastic lesions of the liver: an immunohistochemical study. J Hepatol 2001; 34(6): 850–7.

23. Di Carlo I, Fraggetta F, Lombardo R, Azzarello G, Vasquez E, Puleo S. CD34 expression in chronic and neoplastic liver diseases. Panminerva Med 2002; 44(4): 365–7.
24. Ruck P, Xiao JC, Kaiserling E. Immunoreactivity of sinusoids in hepatocellular carcinoma. An immunohistochemical study using lectin UEA-1 and antibodies against endothelial markers, including CD34. Arch Pathol Lab Med 1995; 119(2): 173–8.
25. Maeda T, Kajiyama K, Adachi E, Takenaka K, Sugimachi K, Tsuneyoshi M. The expression of cytokeratins 7, 19, and 20 in primary and metastatic carcinomas of the liver. Mod Pathol 1996; 9(9): 901–9.

Aušrinė Barakauskienė, Miglė Šumkauskaitė

IMUNOHISTOCHEMIJA DIAGNOZUOJANT HEPATOCELIULINĘ KARCINOMĄ

S a n t r a u k a

Tikslas. Išskiriant hepatoceliulinę karcinomą (HCK) iš kitų kepenų auglių, šiuolaikinėje patologijos diagnostikoje pasitelkiama imunohistochemija. Praktikoje naudojama keletas žymenų, tačiau ne visi jų vienodai naudingi patvirtinant HCK diagnozę. Biopsija gaunamas ribotas audinio pavyzdys, todėl svarbu žinoti, kokie žymenys pagrįstų diagnozę. Mūsų tyrimo tikslas buvo remiantis turimais duomenimis pateikti ekonomiškai pagrįstą imunohistocheminių žymenų rinkinį, naudotiną praktikoje kaip tiksliausiai nurodantį HCK diagnozę bei užtikrinantį minimalias tyrimo išlaidas. Be to, norime pateikti praktikoje naudotiną struktūrizuotą kepenų naviko patologinio tyrimo atsakymą.

Tyrimo medžiaga ir metodai. Tyrimui naudoti 2003–2007 m. Valstybinio patologijos centro duomenys. Į analizę pateko tik tie histologiniai pavyzdžiai, kuriems buvo atliktas imunohistocheminis dažymas: 64 atvejai su patvirtinta HCK diagnoze, 11 – metastazinė adenokarcinoma (MA), 20 – nepiktybiniai kepenų navikai (NKN). HCK buvo grupuojami pagal diferenciacijos laipsnį remiantis Edmondson ir Steiner kriterijais. Preparatai dažyti HepPar1, CD10, CD31, CD34, CK7, CK8 ir CK20 žymenimis.

Rezultatai. HepPar1 teigiama reakcija buvo stebima visuose HCK nepriklausomai nuo naviko diferenciacijos laipsnio: I laipsnio – 52/54 (96,3%), II – 3 (100%), III – 1 (100%); žymens jautrumas – 96,6%, specifiškumas – 100%.

CD10 teigiama reakcija buvo 40 iš 50 HCK atvejų; jautrumas buvo 80%, specifiškumas – 50%. Teigiama reakcija buvo stebima 38 iš 46 gerai diferencijuotų HCK atvejų, 1 iš 3 vidutiniškai diferencijuotų ir 1 iš 1 blogai diferencijuoto. CD10 buvo mažiau specifiškas nei HepPar1 žymuo ($p < 0,002$); gerai diferencijuotuose navikuose teigiama reakcija buvo stebima rečiau ($p<0,01$). CD34 žymens jautrumas buvo 100%, specifiškumas – 97,1%. Lyginant su kitais tirtais žymenimis, šis žymuo buvo jautriausias ($p < 0,05$). CD31 teigiama reakcija buvo stebima visuose navikų preparatuose nepriklausomai nuo jų piktybiškumo, taip pat nebuvo imunohistocheminių reakcijų skirtumų tarp citokeratinų diagnozuojant HCK, MA ir NKN ($p > 0,05$), išskyrus CK7, kurio reakcijos MA preparatuose dažniau nei HCK buvo teigiamos ($p < 0,04$).

Išvados. Praktikoje gali būti naudojami Edmondson ir Steiner supaprastinti HCK histologinės diferenciacijos kriterijai, kurie turėtų būti nurodomi struktūrizuotame patologijos tyrimo atsakyme (synoptic report) kartu su kitais kliniškai svarbiais morfologiniais parametrais.

HepPar1, CD10, CD34 žymenų rinkinio: daugeliu atvejų pakanka HCK diagnozei patvirtinti. HepPar1 yra patikimiausias žymuo HCK diferenciacijai, ypač turint ribotą audinio kiekį. CD34 garantuoja HCK diagnozę ir atskiria nuo tokių nepiktybinių pokyčių, kaip kepenų adenoma ar židininė mazginė hiperplazija. CD10, lyginant su HepPar1, yra mažiau specifiškas, bet jautrus žymuo.

Vertinant naviko neovaskuliarizaciją, CD31 nėra patikimas žymuo, citokeratinų galimybės diferencijuojant HCK taip pat yra ribotos, todėl CD31 ir citokeratinų naudojimas, siekiant patvirtinti HCK diagnozę, nėra tikslingas ir ekonomiškai pagrįstas.

Raktažodžiai: hepatoceliulinė karcinoma, židininė mazginė hiperplazija, hepatoceliulinė adenoma, imunohistocheminiai žymenys