A Comparison of CD10 to pCEA, MOC-31, and Hepatocyte for the Distinction of Malignant Tumors in the Liver

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The distinction of hepatocellular carcinoma (HCC) from metastatic adenocarcinoma (MA) and cholangiocarcinoma (CC) in some cases requires the use of immunohistochemistry. CD10 has recently been suggested as a useful stain for HCC. We directly compared CD10 with other immunohistochemical markers, Hepatocyte, pCEA, and MOC31, that have previously shown to be useful for the distinction between tumors in the liver to help define the current panel of stains that most readily distinguishes HCC from CC and MA. One hundred previously well-characterized tumors in the liver were evaluated and included 25 HCC, 15 CC, and 60 MAs (15 each from breast, esophageal/gastric, pancreatic, and colorectal origin). Tumors were immunostained with the commercially available antibodies Hepatocyte, pCEA, MOC31, and CD10. CD10 stained 13 of 25 HCC and was rarely positive in MA and CC (3/75). Hepatocyte stained 24 of 25 HCC and was negative in all 75 MA and CC. pCEA stained 24 of 25 HCC and 71 of 75 MA and CC with the proper pattern of immunoreactivity, but the pattern of staining was difficult to interpret in several cases. MOC31 stained 1 of 25 HCC and 65 of 75 MA and CC. Hepatocyte was the most sensitive and specific single marker for HCC. CD10 is not a useful addition or substitution to the panel of Hepatocyte, MOC31, and pCEA. The combination of Hepatocyte, MOC31, and pCEA correctly classified 99 of 100 tumors in this study and is our proposed panel of immunostains for the initial workup of malignant tumors in the liver.

KEY WORDS: CD10, Hepatocellular carcinoma, Hepatocyte, MOC31, pCEA.

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The distinction of hepatocellular carcinoma (HCC) from metastatic adenocarcinoma (MA) and cholangiocarcinoma (CC) is often straightforward but can be problematic when either the tumor is poorly differentiated or a small biopsy is submitted. The antibodies that have been suggested as useful in the distinction of hepatocellular carcinoma from metastatic adenocarcinoma and cholangiocarcinoma are numerous and include cytokeratins 7, 8, 18, 19, and 20; alpha-fetoprotein (AFP); Ber-EP4; Factor XIIIa; polyclonal carcinoembryonic antigen (pCEA); and MOC31, among others (1, 2). Previously, the most commonly used markers in this setting were AFP, pCEA, and various cytokeratin subtypes. AFP is noted for its specificity in this setting, but a lack of sensitivity limits its practical use (2, 3). The various cytokeratin subtypes may be useful but show an overlapping pattern of immunoreactivity for HCC and adenocarcinoma (4, 5). The best panel of immunostains for this distinction is constantly changing as more antibodies are added to the list of commercially available immunostains.

MOC31, an antibody directed against a cell surface glycoprotein, has been shown to be useful in distinguishing adenocarcinoma from mesothelioma (6, 7). We have previously shown that MOC31 can be very useful for tumors in the liver; it consistently stains MA and CC but not HCC (8). In addition to being fairly sensitive and specific for adenocarcinoma, the pattern of diffuse and intense plasmalemmal staining with MOC31 is generally easy to interpret.

Polyclonal CEA characteristically stains HCC with a canalicular pattern of immunoreactivity and has a membranous and/or cytoplasmic pattern of immunoreactivity in adenocarcinomas (9). In many cases, pCEA is useful, but the interpretation of the pattern of staining can be difficult. In poorly differentiated HCC, there may not be distinct canalicular

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staining. Intense canalicular staining in HCC may mimic a membranous pattern of immunoreactivity, whereas weak or luminal staining in MA or CC may be misinterpreted as a canalicular pattern.

Another antibody that recently has been shown very useful for the identification of HCC is Hepatocyte, a murine monoclonal antibody that recognizes a not yet fully described epitope in mitochondrial fractions that is the same epitope as that listed for Hep Par 1. Hepatocyte reacts with normal and neoplastic hepatocytes in formalin-fixed paraffin-embedded material with a distinct granular cytoplasmic pattern of immunoreactivity. Previous studies have shown that Hep Par 1 is highly specific for hepatocellular carcinoma (10–12) but does appear to show immunoreactivity with hepatoid adenocarcinomas of the gastrointestinal tract (13). Hep Par 1 has been reported to be both sensitive and specific for HCC but may be less sensitive with poorly differentiated HCC.

Recently, CD10 has been suggested as another marker that stains HCC with a canalicular pattern while rarely staining MA or CC (14, 15). CD10, although certainly not a newly discovered antibody, has only recently been advocated for the distinction of hepatocellular carcinoma from adenocarcinoma. We compare CD10 with other immunohistochemical markers (Hepatocyte, pCEA, MOC31) frequently used to distinguish between HCC and MA or CC and determine whether CD10 is a useful addition or substitution to the panel of immunostains most helpful in this setting.

MATERIALS AND METHODS

Case Material

Formalin-fixed, paraffin-embedded tissue blocks from 100 previously characterized malignant tumors in the liver were retrieved from the archival files of the Department of Pathology at Ohio State University Medical Center, Columbus, Ohio. These 100 previously characterized hepatic neoplasms included 25 HCC, 15 CC, and 15 metastatic tumors from each of the following sites: breast, esophageal/gastric, colorectal, and pancreatic. These 100 cases consisted of 15 needle biopsy specimens (4 breast, 5 colorectal, 3 pancreatic, and 3 esophageal/gastric) and 85 resection specimens; all of the HCC were either wedge resections or partial hepatectomies. Consecutive cases were selected in a retrograde fashion from 2000 to 1987. For all cases of metastatic disease, the primary tumor was reviewed and the diagnosis was verified. For the 25 HCC, tumor grading was performed using the modified criteria of Edmundson and Steiner (16), and tumors were categorized as well, moderately, or poorly differen-

tiated. Poorly differentiated MA and CC without glandular differentiation were recorded.

Immunohistochemical Staining

Immunoperoxidase staining was performed on formalin-fixed, paraffin-embedded tissue cut at 4 μ m and placed on positively charged slides. Slides were then placed in a 60° C oven for 1 hour, cooled, and deparaffinized and were rehydrated through xylenes and graded ethanol solutions to water. All slides were quenched for 5 minutes in a 3% hydrogen peroxide solution in methanol to block for endogenous peroxidase. Antigen retrieval was performed by a heat method for tissue stained with the CD10 (clone 56C6, Novocastra Laboratories Ltd., Newcastle upon Tyne, UK, 1:150) and Hepatocyte (Hepatocyte clone OCH1E5, DAKO, Denmark, 1:150) antibodies, in which the specimens were placed in a citric acid solution (DAKO's Target Retrieval Solution, pH 6.1), for 30 minutes at 94° C using a vegetable steamer. Slides for the pCEA (carcinoembryonic antigen, polyclonal, DAKO, 1:800) and MOC31 (anti-human epithelial related antigen; DAKO, 1:40) antibodies were antigen retrieved using protease for 5 minutes (DAKO'S Proteinase K solution). Slides were then placed on a DAKO Autostainer, immunostaining system, for use with immunohistochemistry. The detection system used was a labeled streptavidin-biotin complex. This method is based on the consecutive application of (1) a primary antibody against the antigen to be localized, (2) biotinylated linking antibody, (3) enzyme-conjugated streptavidin, and (4) substrate chromogen (3,3'-diaminobenzidine). Tissues were avidin and biotin blocked before the application of the biotinylated secondary reagent. Slides were then counterstained in Richard Allen hematoxylin, dehydrated through graded ethanol solutions, and coverslipped.

The slides were reviewed by two pathologists (CM, WLF), and positivity was defined as >1% of cells staining with the proper pattern of reactivity. For Hepatocyte, positive results were interpreted as a distinct granular cytoplasmic pattern of immunostaining that was graded and recorded as 1+ (1 to 5% positive cells), 2+ (5 to 50% positive cells), or 3+ (>50% positive cells). For pCEA and CD10, positive results were interpreted as canalicular, canalicularmembranous, or membranous-cytoplasmic immunostaining. All positive immunoreactivity for MOC31 was plasmalemmal. Positive and negative controls stained appropriately.

RESULTS

HCC were graded as well differentiated in 2 cases, moderately differentiated in 18, and poorly differen-

entiated in 5. Two moderately differentiated HCC had clear cell features. Eleven cases of MA or CC (5 pancreatic, 4 esophageal/gastric, 1 breast, and 1 CC) were poorly differentiated with nests and sheets of neoplastic cells. No hepatoid adenocarcinomas were included in the study. The results of all immunohistochemical stains are summarized in Table 1.

Hepatocyte

Hepatocyte stained 24 of 25 HCC with a cytoplasmic pattern of immunoreactivity (Fig. 1A–B), and no immunoreactivity was seen with CC or MA. For HCC, immunoreactivity for Hepatocyte was 1+ in 6 cases, 2+ in 7 cases, and 3+ in 11 cases. For the six cases of HCC showing 1+ staining, four were poorly differentiated and two were moderately differentiated with clear cell features. The single case of HCC that failed to stain with Hepatocyte was poorly differentiated. The remaining 18 cases of HCC showing 2+ or 3+ staining were well differentiated in 2 cases and moderately differentiated in 16 cases. Table 2 shows the results of Hepatocyte immunoreactivity for HCC with respect to tumor grade. No adenocarcinomas were immunoreactive with Hepatocyte. The sensitivity of Hepatocyte for HCC was 96%, and the specificity was 100%.

Polyclonal CEA

Polyclonal CEA stained 25 of 25 HCC, 15 of 15 CC, 13 of 15 breast MA, 14 of 15 esophageal/gastric MA, 15 of 15 colorectal MA, and 14 of 15 pancreatic MA. Positive staining was canalicular (Fig. 2A) in HCC and membranous and/or cytoplasmic in CC and MA. Twelve cases with immunoreactivity for pCEA were deemed difficult to interpret because of a mixed pattern of immunoreactivity that included 10 cases of HCC and 2 cases of CC. For the 10 cases of HCC (7 moderately and 3 poorly differentiated) with a mixed pattern of immunoreactivity for pCEA, difficulty in interpretation was caused by intense staining resulting in a canalicular-membranous pattern (Fig. 2B). The two cases of CC showed a membranous and luminal pattern of immunoreactivity that could be confused with a canalicular

pattern. For the 10 cases of HCC with a canalicular-membranous pattern of immunoreactivity for pCEA, Hepatocyte was 3+ in 2 cases, 2+ in 6 cases, 1+ in 1 case, and negative in 1 case. For the same 10 cases, CD10 was negative in 7 cases and showed a canalicular, easy-to-interpret pattern in 2 cases and a canalicular-membranous, difficult-to-interpret pattern in 1 case.

MOC31

MOC31 stained 1 of 25 HCC, 14 of 15 CC, 11 of 15 breast MA, 13 of 15 esophageal/gastric MA, 14 of 15 colorectal MA, and 13 of 15 pancreatic MA. Positive staining was strong and diffuse to focal in a plasmalemmal pattern. All cases of adenocarcinoma were positive for pCEA and/or MOC31, including the 11 cases of poorly differentiated MA or CC. The sensitivity and specificity of MOC31 for CC and MA was 87% and 98%, respectively. The one case of HCC that stained with MOC31 was the single case of HCC (poorly differentiated) that failed to stain with Hepatocyte and CD10 and had a canalicular-membranous pattern of immunoreactivity with pCEA. This case was subsequently shown to be positive for AFP and low molecular weight cytokeratin but not cytokeratin 7 and 20 and clinically was consistent with a hepatocellular carcinoma.

CD10

CD10 stained 13 of 25 HCC, 0 of 15 CC, 0 of 15 breast MA, 1 of 15 esophageal/gastric MA, 1 of 15 colorectal MA, and 1 of 15 pancreatic MA. The 13 cases of HCC with positive staining for CD10 showed a canalicular pattern of staining in 8 cases and a canalicular-membranous pattern in 5 cases. The typical pattern of immunoreactivity for CD10 in HCC is shown in Figure 3A–B. The sensitivity and specificity of CD10 for all cases of HCC was 52% and 93%, respectively. The percentage of positive staining HCC with a canalicular-membranous, difficult-to-interpret pattern of immunoreactivity for CD10 (38%; 5 of 13) was similar to the results for pCEA (40%; 10 of 25). The three cases of MA with immunoreactivity for CD10 showed a cytoplasmic pattern

TABLE 1. Immunohistochemical Staining in Hepatic Neoplasms

Neoplasm	Hepatocyte, n (%)	MOC31, n (%)	CD10, n (%)	PCEA, n (%)
HCC (n = 25)	24 (96)	1 (7)	8 ^a (32) 5 ^b (20)	15 ^a (60) 10 ^b (40)
CC (n = 15)	0	14 (93)	0	15 ^c (87) 2 ^b (13)
Breast (n = 15)	0	11 (73)	0	13 ^c (87)
Esophageal/gastric (n = 15)	0	13 (87)	1 ^c (7)	14 ^c (93)
Colorectal (n = 15)	0	14 (93)	1 ^c (7)	15 ^c (100)
Pancreatic (n = 15)	0	13 (87)	1 ^c (7)	14 ^c (93)

^a Canalicular.

^b Canalicular-membranous.

^c Membranous-cytoplasmic.

FIGURE 1. Hepatocellular carcinoma. **A**, hematoxylin and eosin stained section. **B**, cytoplasmic staining with Hepatocyte (40X).

TABLE 2. Hepatocyte Staining in HCC and Tumor Grade

Tumor Grade	Immunoreactivity			
	Negative	1+	2+	3+
Well differentiated (<i>n</i> = 2)	0	0	0	2
Moderately differentiated (<i>n</i> = 18)	0	2	7	9
Poorly differentiated (<i>n</i> = 5)	1	4	0	0

reactivity with these tumors is shown in Figure 4A–E. All cases were negative with Hepatocyte, 10 of 11 stained with MOC31, and 8 of 11 stained with pCEA with the proper pattern of immunoreactivity. CD10 was negative in 9 of 11 cases, and the two positive cases had a cytoplasmic pattern of staining.

of immunoreactivity, including 2 of the 11 cases of poorly differentiated MA or CC.

Poorly Differentiated Adenocarcinoma

The immunohistochemical staining results for the 11 cases of poorly differentiated MA and CC are shown in Table 3. The typical pattern of immuno-

Analysis of Combinations of Immunohistochemical Stains

Table 4 compares the number of cases in which the distinction between HCC and adenocarcinoma was definitive with various combinations of two and three immunohistochemical stains. For a diagnosis to be considered definitive, at least one of the antibodies had to be positive with the proper pat-

FIGURE 2. Hepatocellular carcinoma stained with pCEA. **A**, canalicular pattern of staining. **B**, canaliculo-membranous pattern of immunoreactivity (40 $\times$).

tern of immunoreactivity (for HCC, Hepatocyte, CD10, or pCEA canalicular or canaliculo-membranous; and for adenocarcinoma, MOC31, pCEA cytoplasmic-membranous, or CD10 cytoplasmic). Cases were considered equivocal when no positive immunostaining result was obtained with any of the antibodies considered or results appeared contradictory. The combination of Hepatocyte with CD10 was the least helpful because neither immunostain is typically a positive marker for adenocarcinoma, so most cases remained equivocal, and this combination is not shown in Table 4. The most helpful combination of two antibodies was Hepatocyte with pCEA. When panels composed of three

antibodies were evaluated, the combination of Hepatocyte, pCEA, and MOC31 was superior to the others. Only one case of HCC was not correctly interpreted with this combination of antibodies.

DISCUSSION

In this study we directly compared CD10 with other immunohistochemical markers (pCEA, MOC31, Hepatocyte) that are frequently used to distinguish between HCC and MA or CC. An "ideal panel" of immunostains for the distinction between HCC and adenocarcinoma should include both positive and negative markers for each.

FIGURE 3. Hepatocellular carcinoma. **A**, hematoxylin and eosin stained section. **B**, canalicular pattern of immunoreactivity with CD10 (40×).

TABLE 3. Immunohistochemical Staining in 11 Poorly Differentiated Adenocarcinomas

Location	Hepatocyte	MOC31	CD10	PCEA
CC (<i>n</i> = 1)	0/1	1/1	0/1	1/1
Breast (<i>n</i> = 1)	0/1	1/1	0/1	0/1
Esophageal/gastric (<i>n</i> = 4)	0/4	3/4	1/4	3/4
Pancreatic (<i>n</i> = 5)	0/5	5/5	1/5	4/5

Data indicate number of tumors showing positive staining/total number.

The value of pCEA, MOC31, and Hepatocyte previously has been demonstrated (8–12). Hepatocyte is preferable to AFP as a positive marker for HCC because of its much higher sensitivity than AFP (10, 11). Polyclonal CEA has been traditionally included in panels in this setting because of its ability to act

as a positive stain for both HCC and adenocarcinoma, depending on the pattern of immunoreactivity. MOC31 is another useful marker for the distinction of adenocarcinoma from HCC (8). Therefore, the distinction between HCC *versus* MA or CC with these three antibodies usually results in a combined positive and negative panel of immunostains for interpretation. CD10 has recently been shown to be a positive marker for HCC with a canalicular pattern of immunostaining, and it shows immunoreactivity in some adenocarcinomas with a cytoplasmic pattern (14, 15). We evaluated CD10 with our proposed panel of markers and found that CD10 was not a useful addition or substitution to these immunostains for the distinction of HCC from CC and MA.

FIGURE 4. Immunohistochemical analysis of a poorly differentiated adenocarcinoma. **A**, hematoxylin and eosin stained section. **B**, lack of staining with Hepatocyte. **C**, plasmalemmal pattern of immunoreactivity with MOC31. **D**, cytoplasmic and membranous immunoreactivity with pCEA. **E**, lack of staining with CD10 in tumor cells but canalicular staining in adjacent benign hepatocytes (40 $\times$).

Hepatocyte was extremely sensitive and specific for the detection of HCC with an easy-to-interpret pattern of immunoreactivity. The lack of any staining in MA added to the confidence with which results for Hepatocyte could be interpreted. Therefore, any immunoreactivity for Hepatocyte, no matter how focal, should be considered as positive and highly indicative of HCC. There was a tendency for Hepatocyte not to stain poorly differentiated HCC or areas of clear cell change in as diffuse a manner as well-differentiated to moderately differentiated HCC, which may result in false negatives with needle core biopsies (none of which were included in

our cases of HCC). In our series, Hepatocyte detected almost double the number of HCC as compared with CD10 and, therefore, remains the single most sensitive positive marker for HCC.

The total lack of immunoreactivity for Hepatocyte in all MA and CC, including the 11 cases of poorly differentiated adenocarcinoma, is an important finding. Although Hep Par 1 has been shown to be focally positive in hepatoid adenocarcinomas of the gastrointestinal tract (13), these neoplasms are infrequently encountered by the surgical pathologists. A much more frequently encountered problem is cases of poorly differentiated MA that are

TABLE 4. Number of Cases for Which a Combined Panel of Immunohistochemical Stains Yielded Definitive Results

Neoplasm	CD10 and MOC31	CD10 and pCEA	Hepatocyte and MOC31	Hepatocyte and pCEA	CD10, MOC31, and pCEA	Hepatocyte, pCEA, and CD10	Hepatocyte, MOC31, and CD10	Hepatocyte, pCEA, and MOC31
HCC (<i>n</i> = 25)	14	16	24	25	15	25	25	24
CC (<i>n</i> = 15)	14	13	14	15	14	15	14	15
Breast (<i>n</i> = 15)	14	12	13	12	15	12	14	15
EG (<i>n</i> = 15)	13	14	12	14	15	14	13	15
Colorectal (<i>n</i> = 15)	14	14	14	14	15	14	14	15
Pancreatic (<i>n</i> = 15)	13	14	13	14	15	14	13	15
Total (<i>n</i> = 100)	82	83	90	94	89	94	93	99

EG, esophageal/gastric.

difficult to distinguish from poorly differentiated HCC by H&E characteristics. The lack of staining with Hepatocyte correctly classified all of these cases as MA or CC rather than HCC in our series of 11 cases. However, a negative stain should not be used in isolation when the H&E features are equivocal, and so a positive stain for adenocarcinoma should also be identified. All 11 cases we studied stained positively with pCEA and/or MOC31.

The greatest value of pCEA is that it is a positive marker for both HCC and adenocarcinoma when the proper pattern of staining is identified. Although this is the greatest value of pCEA, it also leads to a shortcoming of this antibody, which is the occasional difficulty in interpretation of the pattern of staining. Although pCEA stained the majority of HCC, the pattern of immunoreactivity was difficult to interpret in half of the cases. When pCEA did show a canalicular pattern of immunoreactivity that was easy to interpret, the results were highly indicative of HCC because this pattern was never identified in any of the CC or MA. It is not prudent to assume that a canalicular-membranous pattern of immunoreactivity with pCEA is absolutely diagnostic of HCC because two cases with staining that mimicked this pattern of immunoreactivity were CC.

Both pCEA and MOC31 were highly sensitive for the detection of adenocarcinoma. Polyclonal CEA detected more adenocarcinomas than MOC31 (71 of 75 with pCEA *versus* 65 of 75 with MOC31). The advantage of MOC31, however, is that the immunoreactivity is easy to interpret because the pattern of staining was plasmalemmal in all cases. Because CD10 was only positive in a few cases of adenocarcinoma, it is not a useful positive stain for adenocarcinoma.

As with all immunohistochemical stains, the findings with a single antibody should be interpreted as part of a panel. One question we addressed was the value of CD10 in situations where the pattern of immunoreactivity with pCEA was difficult to interpret. For those cases of HCC with a canalicular-membranous pattern of immunoreactivity with pCEA (10 HCC and 2 CC), CD10 showed a canalicular pattern of immunoreactivity in 2/10 cases.

Therefore, CD10 may be helpful to clarify a canalicular-membranous pattern of immunoreactivity with pCEA. However, immunostaining with Hepatocyte correctly classified 9/10 of the HCC.

CD10 was negative for a canalicular pattern of immunoreactivity in all MA and CC. This finding is consistent with previous studies evaluating CD10 (14, 15). In addition, CD10 stained only a few cases of MA and CC with a cytoplasmic pattern. A negative result with this antibody by itself is not useful for the distinction of HCC from adenocarcinoma, because 48% of HCC were also negative with CD10. Positive staining for CD10 in a canalicular pattern may be useful for this distinction; however, CD10 is not specific for HCC (17).

The various combinations of two and three antibodies that included a positive marker for both HCC and adenocarcinoma are compared in Table 4. It appears that CD10 with MOC31 or pCEA is the least helpful and that Hepatocyte with pCEA is the most useful combination of two antibodies. The addition of CD10 to any panel of two other antibodies only clarified a few cases, whereas the combination of Hepatocyte, pCEA, and MOC31 was the most useful combination of three antibodies.

The correct diagnosis was achieved in 99 of 100 cases in this study by using a combination of Hepatocyte, MOC31, and pCEA as the preferred panel of immunostains in the initial work-up of hepatic neoplasms. CD10 is a positive marker for HCC but is not a useful addition or substitution to the panel of Hepatocyte, MOC31, and pCEA. Hepatocyte appears at this time to be highly sensitive and specific for HCC, but as in all antibodies, it should be used in a panel because rare cases of adenocarcinoma show immunoreactivity. There remains a very small subset of tumors that are particularly problematic; these may require additional immunostains including CD10, AFP, and various cytokeratins.

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