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Original contribution

Hepatocellular carcinomas can be Special AT-rich sequence-binding protein 2 positive: an important diagnostic pitfall☆,☆☆

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Summary Special AT-rich sequence-binding protein 2 (SATB2) is a sensitive and specific marker for tumors originating with the colon and appendix. It is now commonly used in surgical pathology, while working up carcinomas of unknown primary. We had anecdotally encountered occasional hepatocellular carcinomas (HCCs) that were SATB2 positive. Immunohistochemical expression of SATB2 in HCC has not yet been examined in detail. In this study, we evaluated SATB2 expression in 46 HCCs. Nineteen (41%) of 46 HCCs were positive for SATB2. SATB2 expression in HCCs was more commonly seen in poorly differentiated tumors (11 of 13 cases, 85%) than well and moderately differentiated tumors (8 of 33 cases, 24%), p value = 0.0001. No other statistically significant correlations were observed ($p > 0.05$). There were no other statistically significant correlations between SATB2 expression and age, gender, background liver disease, and cirrhosis ($p > 0.05$). Results of our study show that a significant subset (41%) of HCCs can be SATB2 positive. Awareness of this phenomenon is important as SATB2 expression in a liver tumor does not completely exclude a diagnosis of HCC.

1. Introduction

Special AT-rich sequence-binding protein 2 (SATB2) is a matrix-associated nuclear transcription factor involved in osteoblastic and neuronal differentiation [1,2]. SATB2 has been also shown to be a highly sensitive and specific marker of normal colonic epithelium and colorectal adenocarcinoma [3–5]. It is also considered to be a very good marker for appendiceal and lower gastrointestinal tract well differentiated neuroendocrine tumors [6,7]. SATB2 immunostain is now widely used in surgical pathology, especially while working up carcinomas of unknown primary, as its expression is considered to be highly sensitive for a colorectal or appendiceal primary [8–12]. Of note, SATB2 expression can also be seen within Merkel cell carcinomas, osteosarcomas, and ossifying, as well as non-ossifying peripheral oral fibroma of the gingival region [13–15].

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Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and the sixth most frequent cancer, as well as the fourth leading cause of cancer-related deaths in the world [16]. However, in North America and Europe, metastatic tumors to the liver are much more common than primary hepatic malignancies. Liver is considered to the most common site for cancer metastasis accounting for approximately 25% of all cases, with metastasis from a colorectal primary being the most common [17]. Liver metastasis from colorectal cancer is also one of the major causes of tumor-related deaths in the world [18]. For accurate treatment and patient prognosis, distinguishing HCC from other tumors such as metastatic adenocarcinomas or neuroendocrine tumors is very important. For pathologists, while evaluating hepatic mass lesions, especially on needle biopsies, it is usually valuable to know if the patient has a prior history of malignancy as this information can be useful in recognizing morphological mimickers of HCC. However, many times this clinical information is not readily available and sometimes the patient also may not have a prior known history of malignancy. On hematoxylin and eosin stain, a well differentiated HCC can usually be distinguished from an adenocarcinoma. However, this distinction may not be that easy when dealing with well differentiated neuroendocrine tumors as they can sometimes mimic HCC on morphology, and hence immunostains may need to be used. Similarly, while evaluating tumors with poorly differentiated morphologies, immunohistochemistry usually plays an integral role in distinguishing HCC from metastatic adenocarcinoma or neuroendocrine carcinoma. Immunohistochemistry also plays a vital role in identifying a primary site of origin for a tumor that has metastasized to the liver. In this context, SATB2 is now frequently used, as it is considered to be a sensitive and specific marker for carcinomas arising from the lower gastrointestinal tract [8–12].

We had recently encountered a case of HCC that showed SATB2 staining. Immunohistochemical expression of SATB2 in HCC has not yet been studied in detail. Therefore, we decided to study SATB2 expression in previously diagnosed HCCs at our institution. The aims of this study were to access the frequency and significance of SATB2 in HCCs and to verify if SATB2 expression in a liver tumor can be useful in the exclusion of HCC.

2. Materials and methods

2.1. Case selection and histological review

Forty-six HCCs (15 resections and 31 needle biopsies) between 2017 and 2020 were selected for this study. Institutional review board approved this study. Relevant clinical information was obtained from the patient's medical records. Only unequivocal HCCs were selected for this study. All the cases included in this study were rereviewed to confirm the diagnosis of HCC by assessing the presence of classic morphological features associated with HCC on hematoxylin and eosin sections such as >3 cell thick plates, presence of cytologic atypia, and loss of reticulin framework. Appropriate use of ancillary immunohistochemical markers for hepatocellular differentiation such as HepPar-1, glypican-3, arginase-1, as well as albumin in situ hybridization was performed where necessary. The HCCs were graded into well differentiated, moderately differentiated, or poorly differentiated as per the WHO grading system [16].

2.2. Immunohistochemistry

Immunostains on all cases were performed on a 4-micron formalin-fixed paraffin-embedded tissue section using SATB2 antibody (EP281, ready to use, rabbit monoclonal, Cell Marque, Rocklin, CA) on a Ventana Benchmark Ultra using the Ultra View DAB detection kit (Ventana Medical Systems, Inc., Tucson, AZ). The protocol included standard heat retrieval of 36 min @ 95°C using an 8.9pH buffer. The antibody incubation was for 32 min @ 37°C. Immunohistochemical staining was evaluated by two pathologists (W.L. and V.S.C.). Only moderate to strong intensity of nuclear staining within the neoplastic cells was considered positive. The SATB2 immunostain was semiquantitatively graded as negative (no positive cells), 1+ (<10% positive cells), 2+ (11–25% positive cells), 3+ (26–50% positive cells) or 4+ (>51% positive cells). SATB2 expression within the tumor was correlated with clinicopathological features.

2.3. Statistical analysis

Chi-square test was used to compare the data between the different groups, and the difference was considered significant if the p-value was ≤ 0.05.

3. Results

3.1. Clinical and histological features

The clinical and pathological characteristics of HCCs included in this study are summarized in Table 1. There were 38 men and 8 women (age range: 44–84 years; median age: 67 years). The background chronic liver disease was hepatitis B virus in 5 cases (11%), hepatitis C virus in 22 cases (48%), both hepatitis B and C viruses in 2 cases (4%), alcoholic liver disease in 6 cases (13%), non-alcoholic liver disease in 2 cases (4%), and hereditary hemochromatosis, as well as alpha-1-antitrypsin deficiency, in 1 case (2%) each. There was no known chronic liver disease in 7 cases (16%). Twenty-seven (59%) of HCCs arose within a cirrhotic liver. Three (7%) of HCCs were well differentiated, 30 (65%) were moderately differentiated, and 13 (28%) were poorly differentiated tumors. Majority of HCCs (43/46, 93%) were of conventional type, whereas 3 (7%) were steatohepatitic subtype of HCC.

Table 1 SATB2 expression in hepatocellular carcinomas.

Characteristics	SATB2 positive n = 19 (41%)	SATB2 negative n = 27 (59%)	p value
Age (yr)			0.228
≤50	1 (5%)	0	
>50	18 (95%)	27 (100%)	
Gender			0.809
Male	16 (84%)	22 (81%)	
Female	3 (16%)	5 (19%)	
Background liver disease			0.187
Hepatitis B virus	3 (16%)	2 (7%)	
Hepatitis C virus	8 (42%)	14 (52%)	
Hepatitis B and C viruses	0	2 (7%)	
Non-alcoholic steatohepatitis	0	2 (7%)	
Alcoholic liver disease	5 (26%)	1 (4%)	
Alpha-1-antitrypsin deficiency	0	1 (4%)	
Hereditary hemochromatosis	0	1 (4%)	
Unknown	3 (16%)	4 (15%)	
Differentiation			0.0001[a]
Well differentiated	1 (5%)	2 (7.5%)	
Moderately differentiated	7 (37%)	23 (85%)	
Poorly differentiated	11 (58%)	2 (7.5%)	
Background cirrhosis			0.483
Present	10 (53%)	17 (63%)	
Absent	9 (47%)	10 (37%)	

HCC, hepatocellular carcinoma; SATB2, special AT-rich sequence-binding protein 2.
[a] p value was calculated by combining well differentiated and moderately differentiated HCC versus poorly differentiated HCC.

3.2. SATB2 expression in HCCs

Table 1 summarizes the details of SATB2 expression within our study. Nineteen (41%) of 46 HCCs were positive for SATB2 (Fig. 1B). Of these 19 positive cases, 1 (5%) was well differentiated, 7 (37%) were moderately differentiated, and 11 (58%) were poorly differentiated (Fig. 1A). Background cirrhosis in the SATB2 positive cases was seen in 10 (53%) cases. The background liver disease was hepatitis C in 8 (42%), alcoholic liver disease in 5 (26%), hepatitis B in 3 (16%), and unknown in 3 (16%) cases. The SATB2 expression was scored as 1+ in 5 cases (1 well differentiated, 1 moderately differentiated, and 3 poorly differentiated), 2+ in 6 cases (3 moderately differentiated and 3 poorly differentiated), 3+ in 2 cases (both moderately differentiated), and 4+ in 6 cases (1 moderately differentiated and 5 poorly differentiated). Arginase-1 immunostain was positive in all 19 cases (Fig. 1C), including the areas within the tumors that were SATB2 positive. HepPar-1 immunostain was performed in 5 cases, and it was also positive in all 5 cases including the areas that showed SATB2 expression. Glypican-3 immunostain was performed in 15 cases, and it was positive in 12 cases (Fig. 1D). There was no positive staining for SATB2 in the background non-neoplastic liver parenchyma, when present on the stained sections. Poorly differentiated HCCs (11 of 13 cases, 85%) showed significantly more expression of SATB2 than well and moderately differentiated tumors (8 of 33 cases, 24%), p value = 0.0001. There were no other statistically significant correlations ($p > 0.05$) between SATB2 expression and age, gender, background liver disease, and cirrhosis. One of the 3 steatohepatitic subtype of HCC showed positive staining for SATB2.

4. Discussion

The liver is a recipient of dual blood supply from the systemic (arterial) and portal (venous) systems, making it one of the most common sites in the body for hematogenous metastasis. Approximately 20% of patients with colorectal cancer present with distant metastasis at the time of initial diagnosis [19]. Liver is also the most common site of metastasis for patients with colorectal adenocarcinoma [20]. SATB2 is now a commonly used immunohistochemical marker in surgical pathology, as a sensitive and specific marker for colorectal and appendiceal adenocarcinomas. Along with CDX2, SATB2 is considered to be a useful supplementary marker in the diagnosis of colorectal carcinoma during workup for a carcinoma of unknown primary [21–23].

The results of our study show that 19 of 46 HCCs (41%) were positive for SATB2. Two prior studies have also

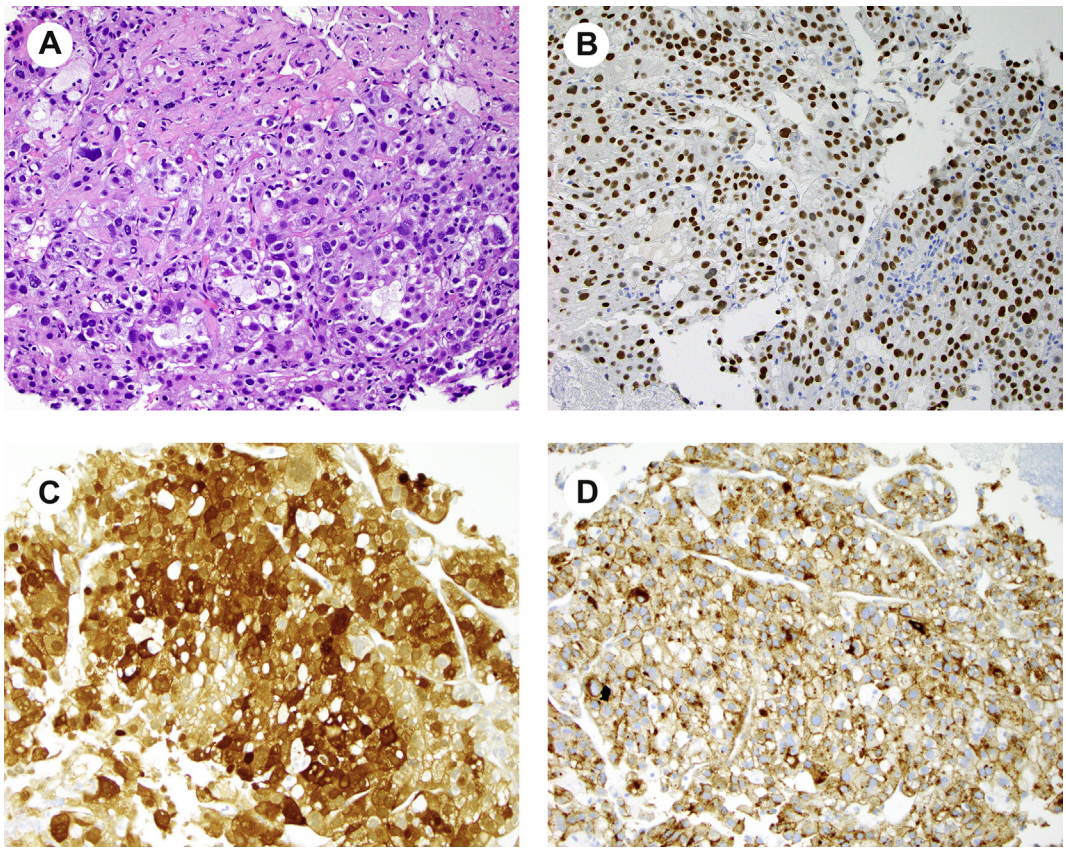

Fig. 1 Poorly differentiated hepatocellular carcinoma. (A) H&E stain showing tumor cells with eosinophilic cytoplasm and large pleomorphic nuclei (200x). (B) SATB2 showing nuclear expression (200x). (C) Arginase-1 immunostain is positive within the tumor (200x). (D) Glypican-3 immunostain is also positive within the tumor (200x). SATB2, special AT-rich sequence-binding protein 2.

briefly described SATB2 expression in HCCs [22,24]. Mochizuki et al. [22] reported SATB2 expression in 27% (8 of 30) HCCs, while accessing the use of SATB2 for diagnosing carcinoma of unknown primary origin. Another study by Li et al. [24] performed on tissue microarray specimens showed SATB2 expression in 7% (5 of 67) HCCs. However, SATB2 expression within HCCs was not the primary focus of either articles, and they did not provide any significant details about the degree and intensity of SATB2 expression in HCCs or its correlation with the type and histological differentiation/grade of HCC. Hence, we sought to systematically evaluate SATB2 expression in HCCs.

Colonic adenocarcinomas are usually strongly and diffusely positive for SATB2. However, a subset of colonic adenocarcinomas (up to 10−20%) can show patchy to focal staining of moderate to weak intensity, including those associated with DNA mismatch repair protein deficiency and BRAF mutation [22,23,25,26]. Similarly inflammatory bowel disease associated colorectal adenocarcinomas can show significantly lower degree of staining for SATB2 when compared with colorectal adenocarcinomas arising in a sporadic setting [27,28]. Studies have also shown that a subset of metastatic colorectal adenocarcinomas to the liver can show focal to patchy SATB2 staining of moderate to weak intensity [23,29]. In our study, of the 19 HCCs that were SATB2 positive, 5 showed 1+ staining (<10% positive cells), 6 showed 2+ staining (11−25% positive cells), 2 were 3+ (26−50% positive cells), and 6 were 4+ (>51% positive cells).

The main practical point of our study is, to not completely exclude the possibility of HCC, just because a liver tumor is positive for SATB2. Of course, whether or not this becomes a problem would highly depend on the morphological characteristics of a particular case, the immunohistochemical approach taken, and the differential diagnosis generated by the pathologist. SATB2 expression in well to moderately differentiated HCCs may not be an issue due to the typical morphological findings of the tumor, and SATB2 immunostain would not be typically used in the immunohistochemical workup of such tumors. However, sometimes well differentiated neuroendocrine tumors can mimic HCC on morphology. In such a scenario, SATB2 may be included within a panel of immunostains by a surgical pathologist, as SATB2 has also been shown to be a sensitive and specific marker of well differentiated neuroendocrine tumors originating within the appendix and rectosigmoid colon [6,7].

On the other hand, when poorly differentiated tumors involve the liver, the immunohistochemical workup may include SATB2 to exclude the possibility of metastatic colorectal adenocarcinoma to the liver. In our study, majority of the poorly differentiated HCCs (11 of 13, 85%) showed SATB2 positivity. Of note, 6 of these 11 tumors showed 4+ positivity (>51% positive cells). Therefore, it is critical for pathologists to be aware that HCCs can show SATB2 expression, as it can reduce the potential for misdiagnosis of these tumors as non-HCCs.

Dysregulation of microRNAs (miRs) have been known to be involved in carcinogenesis of various organs. MiR-211 has been shown to be a tumor suppressive in HCC tumorigenesis by inhibiting cell proliferation and migration of HCC cell lines [30]. SATB2 has been shown to be a direct target of miR-211 to inhibit cell proliferation and invasion of HCC cells [30]. The miR-211 levels inversely correlate with the SATB2 levels in HCC, and SATB2 has been shown to rescue the miR-211−mediated inhibition of cell invasion and proliferation [30]. High expression of SATB2 in HCC tissues and cell lines has also been shown to correlate with poor prognosis and aggressive clinical phenotype [31]. A recent study has also shown that SATB2 is an oncogenic factor, showing higher expression in HCC cells derived from African Americans when compared with those from Caucasian Americans, accounting for disparity in HCC outcomes between the two groups [32]. SATB2 has also been suggested to be a crucial upregulator of HCC, and it may also be potential therapeutic target for HCC [31]. Hence, it is possible that immunohistochemical expression of SATB2 in a subset of HCCs may be marker of poor prognosis. Future studies, involving a larger number of cases may be useful to accurately evaluate the prognostic significance of SATB2 expression in HCCs. Of note, the results of our study showed that SATB2 expression appears to be more common in poorly differentiated HCCs than well and moderately differentiated HCCs ($p < 0.0001$).

SATB2 may also have a role in the development and prognosis of other cancers too. Recent studies in breast, colorectal, and pancreatic cancer models have shown that SATB2 gene can transform normal epithelial cells to cancer stem-like cells, with significantly higher expression of SATB2 in cancer tissues when compared with normal counterparts [33−35]. Studies have also shown that high levels of SATB2 expression in colorectal cancers may serve as indicator for moderate sensitivity to chemoradiation, as well as an independent marker for good prognosis [4,36]. Reduced SATB2 expression in clear cell renal cell carcinoma has also been associated with metastasis and poor prognosis [37].

The limitations of our study include the retrospective design, relatively small number of cases by some standards, and combining HCC specimens obtained via both needle biopsy and resections for SATB2 evaluation. We included needle biopsy specimens in this study, as liver is a unique site, and many of the liver biopsies obtained from a mass lesion show metastatic disease. In such a setting, a panel of immunohistochemical stains that may include SATB2 is a commonly used approach for initial tumor classification. In addition, in our study, roughly an equal percentage of HCCs showed positive SATB2 staining both on resections (6/15, 40%) and needle biopsies (13/31, 42%), suggesting that SATB2 expression on HCCs obtained via needle biopsies adequately reflects SATB2 expression in resection specimens.

In summary, even though SATB2 remains a highly sensitive and specific marker of lower GI tract origin in tumor pathology, our study demonstrates that a subset of HCCs (41%) can be SATB2 positive. Of note, a majority of poorly differentiated HCCs (11 of 13, 85%) in our study were SATB2 positive. SATB2 expression in a liver tumor does not completely exclude HCC and awareness of this phenomenon is important. Appropriate immunohistochemical workup with immunostains such as arginase-1, HepPar-1, and glypican-3 which are specific for hepatocellular lineage should be pursued in SATB2-positive liver tumors, particularly in poorly differentiated tumors or even in patients with a known past history of colorectal adenocarcinoma or neuroendocrine tumor, to avoid the possibility of missing a diagnosis of HCC.

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All authors listed have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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