Cytologic Features and Histologic Correlations of Microacinar and Microtrabecular Types of Well-Differentiated Hepatocellular Carcinoma in Fine-Needle Aspiration Biopsy

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BACKGROUND. Well-differentiated hepatocellular carcinoma (HCC) in fine-needle aspiration (FNA) biopsy is characterized by trabeculae three or more cells thick wrapped by peripheral endothelium. The authors encountered another pattern that did not fulfill these classic criteria for malignancy yet was proven to be HCC in clinical follow-up. The objective of this study was to characterize the cytologic features of this pattern with histologic correlations.

METHODS. Over a period of 6.5 years, 14 of 123 cases (11.4%) of HCC from 428 liver aspirates showed the unusual pattern. Their cytologic features were compared with 14 cases of nonneoplastic liver on FNA smears that were processed with Ultrafast Papanicolaou stain, and their histologic features were compared on cell blocks with hematoxylin and eosin stain and reticulin stain.

RESULTS. The unusual type of well differentiated HCC in FNA smears was characterized by numerous, small hepatocytes with minimal nuclear atypia but reduced cytoplasm, grouped together in microacini of five or more cells and microtrabeculae one or more cells thick of irregular thickness with no apparent peripheral endothelium. Transgressing capillaries were found when the smears were inspected carefully. In histology nine cases that were the compact type of HCC, two cases that were the microacinar type of HCC, and three cases that were the microtrabecular type of HCC. All FNAs showed deficient reticulin framework. All 14 cases of nonneoplastic liver aspirate were characterized by the presence of large tissue fragments that were resistant to smearing.

CONCLUSIONS. Well differentiated HCC may present as microtrabeculae of irregular thickness one or more cells thick with inapparent peripheral endothelium or as microacini mimicking neuroendocrine carcinoma.

KEYWORDS: well-differentiated hepatocellular carcinoma, compact type of hepatocellular carcinoma, solid type of hepatocellular carcinoma, small cell dysplasia.

Cytologic diagnosis of mass lesions of the liver by transabdominal fine-needle aspiration (FNA) biopsy is a more sensitive and less invasive method with a lower complication rate compared with core needle biopsy. A well recognized difficulty in FNA cytology arises at the end of the malignant spectrum, with a differential diagnosis of very well-differentiated hepatocellular carcinoma (HCC) from nonneoplastic, benign, macroregenerative liver nodules. The majority of HCC shows a trabecular growth pattern, an important feature for the diagnosis of well-differentiated HCC. Histologically, the trabecu-
The diagnostic criteria for well-differentiated HCC in FNA cytology was described as early as 1984 and has been confirmed by numerous studies. Well-differentiated HCC is characterized by a hypercellular smear comprised of trabeculae of three or more cells wrapped by peripheral endothelium. We encountered an unusual type of well differentiated HCC with cytologic features that did not fulfill these diagnostic criteria yet was proven to be HCC in clinical follow-up. The objective of the current study was to accumulate a series of such cases and then characterize their cytologic and histologic features.

MATERIALS AND METHODS

All FNA biopsies of the liver were performed under ultrasound guidance by radiologists using a 10-inch-long, 22-gauge needle. In seven patients, the radiologist also performed a 14-gauge needle core liver biopsy for surgical pathology. A cytotechnologist was present on site to make Swedish-style, oval smears on clear microscopic slides, which were then air dried. At least one smear from each pass was stained with Quick-Dip stain (Mecedes Medical, Sarasota, FL) for the assessment of the adequacy of sample. The remaining air-dried smears were brought back to the laboratory for Ultrafast Papanicolaou stain (Richard Allan Scientific, Kalamazoo, MI). A dedicate pass comprised of several 22-gauge, fine-needle cores also was performed for the preparation of cell blocks. In addition to hematoxylin and eosin staining, the cell block paraffin sections also were used for reticulin stain. In difficult cases, immunohistochemical stains, including CD34, polyclonal carcinoembryonic antigen (CEA), Hepar-1, and MIB-1, also were performed using the standard avidin-biotin-peroxidase method.

Every percutaneous FNA biopsy the first author examined at the Cytopathology Laboratory of New York University Medical Center since 1996 was documented. Of 428 liver FNAs, 123 cases were HCC and 14 cases (11.4%) were so well-differentiated that they did not meet the classic criteria of malignancy yet were proven to be HCC by long-term follow-up.

RESULTS

Clinical Information and Cytologic Diagnosis

The age of the 14 patients with the unusual type of well-differentiated HCC ranged from 49 to 82 years (mean, 64.4 years). Twelve patients were male and two patients were female. All but one patient had cirrhosis. Six patients had hepatitis C, one patient had hepatitis B, one patient had primary sclerosing cholangitis, and six patients had cirrhosis of uncertain etiology. Magnetic resonance images (MRI) and computed tomography (CT) scans showed solid, hypervascular masses with radiologic characteristics of HCC. Eleven patients presented with a solitary mass and three patients presented with multifocal masses. The size of the liver mass ranged from 2.5 cm to 9.5 cm (mean, 4.2 cm). Initially, the diagnoses on FNA smears were difficult, ranging from benign hepatocytes, to atypical hepatocytes, to carcinoid. The diagnoses improved as experience accumulated. Of the 14 cases, one was reported as benign hepatocytes, one was reported as carcinoma with neuroendocrine features, four were reported as hepatocellular neoplasm of borderline malignant potential, and eight were reported as well-differentiated HCC. Follow-up showed all 14 patients had HCC. The relevant clinical history, radiologic findings, histology, FNA diagnosis and core biopsy diagnosis, and follow-up information are summarized in Table 1.

Cytologic Findings

Compared with the broad trabeculae of the classic type of well-differentiated HCC (Figs. 1A and 1B and Fig. 2A), the unusual types are comprised of microtrabeculae (Figs. 1C and 1D) and microacini (Figs. 1E and 1F). The microtrabeculae frequently are branched, with the narrowest regions only one or two cells thick, and the microacinar structure frequently comprised of as few as five or six cells. The microtrabeculae and microacini appear naked with inapparent peripheral endothelium and require CD34 antibody to demonstrate their patchy distribution (Fig. 2B). Transgressing capillaries are present but require searching (Fig. 1C). Seven cases presented with a predominant microtrabecular pattern. Four cases presented with a predominant microacinar pattern. Two cases presented with approximate equal proportions of microacinar and microtrabecular components. One case presented with numerous, single cells with eccentric cytoplasm and several nucleoli and occasional microacini, mimicking neuroendocrine carcinoma. However, the neuroendocrine markers were negative, and polyclonal CEA marked the lumen of the microacini as canaliculi (Fig. 1F, inset) in the concurrent needle core biopsy. The neoplastic hepatocytes uniformly were small with a high nucleus/cytoplasmic ratio, resulting from a reduction of cytoplasm rather than increased nuclear size. The majority of nuclei in the small hepatocytes contained small but distinct, single nucleolus. The cytologic features of each patient are listed in Table 2. The tissue fragments from all 14 nonneoplastic liver aspirates were difficult to smear apart and remained
in large, cohesive tissue fragments (Fig. 1G). A few of the hepatic plates broke off from the smearing and appeared as flat, polyhedral cells with abundant, granular cytoplasm, sharp cell borders, and mostly central nuclei. The cells were heterogeneous with a variety of nuclear sizes and features (Fig. 1H). Intact reticulin fibers along a single plate of hepatocytes were present in nonneoplastic liver aspirates (Fig. 2C).

### Histologic Correlations

In histology, nine cases were the compact type (Figs. 2E and 2F), two cases were the microacinar type, and three cases were the microtrabecular type of HCC. All showed a deficient reticulin framework (Fig. 2D).

### DISCUSSION

In the World Health Organization classification\(^9,25\) of HCC, there are a number of histologic variants of HCC, including the microacinar pattern, formed by the dilated canaliculi, and the compact (solid\(^26\)) growth pattern, formed by the trabeculae growing together, compressing the sinusoids and forming sheets of tumor cells. The majority of microacinar and microtrabecular types of HCC in cytology were the compact type of HCC in histology in this study.

The microtrabecular and microacinar types of HCC on FNA biopsy are characterized by monotony of the neoplastic hepatocytes with little variation in nuclear features, which appear normal in size, shape, and chromasia, but with marked reduction of cytoplasmic size, resulting in small hepatocytes with high a nucleus/cytoplasmic ratio as well as nuclear crowding. One to three-cell-thick, microtrabecular cell arrangements are not new in liver cancers and have been reported in 31% of children with a pure, fetal

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### TABLE 1

Clinical Data on the Microtrabecular and Microacinar Types of Well Differentiated Hepatocellular Carcinoma in Fine-Needle Aspiration Biopsy

| Patient | Age (yrs) | Gender | Cirrhosis (etiology) | Radiology | Histology* (cell block) | FNA diagnosis | Needle core diagnosis | Follow-up |
|---------|-----------|--------|----------------------|-----------|-------------------------|---------------|----------------------|-----------|
| 1       | 53        | Male   | Yes (uncertain)      | Solitary, 6.5 cm, † vascularity | Compact (solid) type | Benign       | Cirrhosis            | Bone metastasis 2 mos later |
| 2       | 50        | Male   | Yes (hepatitis C)    | Solitary, 3.0 cm, † vascularity | Compact type         | Borderline    | Cirrhosis            | HCC (liver transplant) |
| 3       | 79        | Female | Yes (uncertain)      | Multifocal throughout liver, † vascularity | Compact type         | HCC          | HCC                  | Died of pneumonia 2 weeks later |
| 4       | 64        | Male   | Yes (hepatitis C)    | Solitary, 4.7 cm, † vascularity | Compact type         | Borderline    | Cirrhosis            | Bone metastasis 3 yrs later |
| 5       | 62        | Male   | Yes (alcohol abuse)  | Solitary, 3.0 cm, † vascularity | Compact type         | Borderline    | Not done             | HCC (partial hepatectomy) |
| 6       | 50        | Male   | Yes (hepatitis C)    | Solitary, 2.5 cm, † vascularity | Compact type         | HCC          | Not done             | HCC (liver transplant) |
| 7       | 75        | Male   | Yes (hepatitis B)    | Solitary, 3.0 cm, † vascularity | Compact type         | HCC          | Cirrhosis            | Chemoembolization |
| 8       | 49        | Male   | No cirrhosis         | 9.5 cm and satellites, † vascularity | Microacinar type     | Carcinoma with NE features | HCC, microacinar | Adrenal metastasis 6 mos later |
| 9       | 54        | Male   | Yes (hepatitis C)    | Solitary, 3.0 cm, † vascularity | Compact type         | HCC          | Not done             | Refused treatment, died from peritonitis |
| 10      | 75        | Male   | Yes (uncertain)      | Solitary, 3.2 cm, † vascularity | Compact type         | HCC          | Not done             | Chemoembolization |
| 11      | 77        | Male   | Yes (PSC)            | Solitary, 5.5 cm, † vascularity | Microtrabecular (two cells thick) | HCC          | Cirrhosis            | HCC (partial hepatectomy) |
| 12      | 74        | Female | Yes (uncertain)      | > Ten nodules, 2.6 cm, † vascularity | Microtrabecular (two cells thick) | HCC          | Not done             | Disease progression |
| 13      | 58        | Male   | Yes (hepatitis C)    | Two nodules, 4 cm, † vascularity | Microacinar type     | HCC          | Not done             | HCC (liver transplant) |
| 14      | 82        | Male   | Yes (uncertain)      | Solitary, 8.0 cm, † vascularity | Microtrabecular (two cells thick) | Borderline    | Not done             | Satellite nodules 1 yr later |

FNA: fine-needle aspiration; † vascularity: increased vascularity; HCC: hepatocellular carcinoma; borderline: hepatocellular neoplasm of borderline malignant potential; NE: neuroendocrine; PSC: primary sclerosing cholangitis.

* Based on the 2000 World Health Organization subclassification of hepatocellular carcinoma.

b Size of largest nodule.
FIGURE 1. Fine-needle aspiration smear patterns of liver and subtypes of well differentiated hepatocellular carcinoma (HCC). Top row: Classic pattern. (A) Numerous, sharply delineated, broad trabeculae that were separated easily by the smearing. (B) The sinusoidal, endothelium-wrapped macrotrabeculae are comprised of a monotonous population of round cells with prominent, single nucleolus; small amounts of cytoplasm; and inconspicuous cell borders. Second row: Microtrabecular pattern. (C) Numerous microtrabeculae that were separated easily by the smearing. The open arrow points to a transgressing capillary. The solid arrow points to a branching microtrabeculae that is enlarged in D and reveals the absence of peripheral endothelial wrapping and the narrowest part of one or two cells. Note the monotony of the small hepatocytes with sharp borders and single nucleolus. Third row: Microacinar pattern. (E) Numerous microacini that were separated easily by the smearing. (F) Two naked microacini comprised of monotonous, small, uniform hepatocytes with indistinct cell borders and eccentric nuclei with single nucleolus. (Inset) The intraluminal canaliculus of a microacinus is labeled by polyclonal carcinoembryonic antigen antibody. Bottom row: Nonneoplastic liver. (G) Large tissue fragments that were difficult to smear apart due to the intact reticulin network. Note the retraction halo around the tissue fragments that resulted from an air-dry rehydration artifact. (H) The flat sheet of polyhedral cells has ample cytoplasm and sharp borders. The central nuclei show subtle variation in size and features. Note the glycogenated nuclei near the center (Ultrafast Papanicolaou stain). Original magnification × 40 (left column); × 400 (right column).
FIGURE 2. Special stains and histology of hepatocellular carcinoma (HCC) with microtrabecular and microacinar smear patterns. (A) CD34-immunostained control section (using HCC with the classic smear pattern) showing continuous, sinusoidal endothelium wrapping around the broad trabeculae. (B) HCC with a microtrabecular smear pattern showing sparse endothelial wrapping. (C) Reticulin stain of nonneoplastic liver showing the intact reticulin framework surrounding one-cell plate architecture. (D) HCC with microacinar smear pattern showing defective reticulin framework around neoplastic hepatocytes. This was Patient 1 with bone metastasis. Cell blocks of HCC with a predominant microtrabecular pattern (E) and a predominant microacinar smear pattern (F). Cell block sections with CD34 stain (A,B), reticulin stain (C,D) and hematoxylin and eosin stain (E,F). Original magnification \( \times 100 \) (A,B,E,F); \( \times 400 \) (C,D).

TABLE 2
Cytologic Features of the Microtrabecular and Microacinar Types of Hepatocellular Carcinoma

| Patient | Architecture | Cytoplasm size | Cell border | Nuclear size | Location of nuclei | Nucleoli size | Nucleoli no. | Comment |
|---------|--------------|----------------|-------------|--------------|-------------------|--------------|-------------|---------|
| 1       | A            | Indistinct     | Normal      | Eccentric    | Small             | Single       | See Figure 1E,F |
| 2       | T            | Sharp          | Normal variation | Eccentric  | Small             | Multiple     | Miniature hepatocytes |
| 3       | T            | Sharp          | Normal      | Central      | Small             | Single       | See Figure 1C,D |
| 4       | Mixed        | Sharp          | Normal      | Central      | Small             | Multiple     | —           |
| 5       | T            | Sharp          | Normal      | Central      | Small             | Single       | —           |
| 6       | A            | Sharp          | Normal      | Variable     | Small             | Multiple     | —           |
| 7       | Mixed        | Sharp          | Normal      | Central      | Macro             | Single       | —           |
| 8       | A and single | Indistinct     | Normal      | Eccentric    | Small             | Multiple     | NE          |
| 9       | A            | Indistinct     | Normal      | Variable     | Macro             | Single       | Nuclear inclusions |
| 10      | T            | Indistinct     | Normal      | Central      | Small             | Single       | Fatty change |
| 11      | T            | Sharp          | Normal      | Central      | Small             | Single       | —           |
| 12      | T            | Marked         | Indistinct  | Normal      | Eccentric        | Small        | Several     |
| 13      | A            | Distinct       | Normal      | Eccentric    | Small             | Single       | —           |
| 14      | T            | Indistinct     | Normal      | Central      | Small             | Single       | —           |

A: microacini predominant; T: microtrabeculae predominant; ↓: decreased; mixed: approximately equal microacinar and microtrabecular components; single: numerous dysplastic single cells with retained cytoplasm; NE: neuroendocrine cytologic features.
TABLE 3
Cytologic Features of the unusual types of Well-Differentiated Hepatocellular Carcinoma and Histologic Basis

| Cytologic features                        | Histologic basis                                                                 |
|-------------------------------------------|----------------------------------------------------------------------------------|
| Separated trabeculae and microacini in smears | Decreased reticulin framework around the neoplastic hepatocytes allowing the trabeculae or acini to be separated by the force of smearing |
| Transgressing capillaries                  | Neangiogenesis                                                                    |
| Trabecule of irregular thickness           | Loss of the single cell plate architecture                                         |
| Microtrabeculae (≥ 1 cell thick)           | Fetal trabecular                                                                  |
| Microacini                                 | Neoplastic hepatocytes surround dilated canaliculi                                 |
| Reduction of cytoplasm                     | Small cell change                                                                 |

epithelial pattern of hepatoblastoma. Likewise, the microacinar pattern of HCC has been reported as an acinar pattern in many cytologic studies. In fact, nearly all the unusual cytologic features of HCC described in this study have been reported previously in the cytologic literature, including high cellularity, cell dissociation, monotonoty, narrow trabeculae, uniform prominent nucleoli, absence of macronucleoli, multiple nucleoli, small cell size, decreased cytoplasm, increased nucleus/cytoplasmic ratio, nuclear crowding, polygonal cells resembling normal hepatocytes with central nucleoli, and eccentric nuclei, as well as the compact histologic type of HCC. Pitman and Szyfelbein reported that 2 of 35 cases of HCC (5.7%) failed to contain peripheral endothelium, and 1 case was well-differentiated HCC. The current study confirms all of these previous findings and summarizes these cytologic features in a series of 14 cases with histologic correlation (Table 3).

When encountering small hepatocytes arranged in a microtrabecular and microacinar smear pattern, it is important to find out the size of the liver mass from radiology, because small cell dysplasia has similar cytologic and histologic features. Nodules smaller than a certain size will be regarded by surgical pathologists as small cell dysplasia, and nodules larger than a certain size will be regarded as a compact type of HCC. The opinions regarding nodule size sometimes is not conspicuous, and CD34 immunostaining may be required to highlight the peripheral endothelium outlining the trabeculae (Fig. 2A), and the status of the reticulin framework requires reticulin stain for assessment (Fig. 2, C,D).

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