Focus on Dysplastic Nodules and Early Hepatocellular Carcinoma: An Eastern Point of View

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Although increasing numbers of equivocal nodular lesions have been detected in patients with liver cirrhosis with the development of various diagnostic imaging modalities, the pathological diagnosis of small, well-differentiated hepatocellular carcinoma (HCC) in the early stage and of high-grade dysplastic nodules (DNs) is a controversial issue among both Japanese and Western pathologists. In particular, many of the vaguely nodular HCCs of well-differentiated HCC diagnosed by Japanese pathologists tend to be interpreted as high-grade DNs rather than HCC by Western pathologists. In contrast, many of the high-grade DNs diagnosed by Western pathologists are interpreted as well-differentiated HCC by Japanese pathologists. The reasons for the discrepancy between Japanese and Western pathologists can be explained by the following: for Western pathologists, most information comes from the study of HCC and advanced cirrhosis explanted at liver transplantation without detailed clinical information about the nodules; for Japanese pathologists, most information comes from the examination of surgical and biopsy materials together with detailed clinical information that includes meticulous follow-up data on the clinical course of the nodular lesions. To resolve the diagnostic confusion concerning equivocal nodular lesions in the cirrhotic liver, it is necessary to promote the active exchange of clinicopathologic information between Japan and Western countries. (Liver Transpl 2004;10:S3–S8.)

Along with the popularization of various diagnostic imaging modalities and the establishment of follow-up systems for populations at high risk for hepatocellular carcinoma (HCC), such as hepatitis-virus-related cirrhosis, increasing numbers of small nodular lesions have been detected. Although many of these nodular lesions are HCC, equivocal nodules in which it is difficult to determine well-differentiated HCC or high-grade dysplastic nodules (DNs) are also increasing. These equivocal nodular lesions have attracted the attention of both pathologists and clinicians in terms of hepatocarcinogenesis, but the topic was not a matter of interest for Western pathologists until some years ago because of the relatively low frequency of HCC in their countries. Since liver transplantation has become popular as the ultimate treatment for advanced liver cirrhosis and HCC, Western pathologists have increasingly experienced equivocal nodular lesions in explanted livers with the result that these lesions are now in the spotlight. At present, however, the pathological diagnosis of small, well-differentiated HCC in the early stage and of high-grade DNs is a controversial issue among Japanese and Western pathologists.

In this article, the author describes the pathomorphologic characteristics of HCC in the early stage according to the Japanese experience and the confusion in the pathological interpretation of early HCC and DNs among Japanese and Western pathologists.

Pathology of Well-Differentiated HCC in the Early Stage

Morphological Characteristics

In Japan, small HCCs up to about 2 cm in diameter are classified into 2 types according to gross features (Fig. 1): small HCC of distinctly nodular type and small HCC of vaguely nodular type. Small HCCs of distinctly nodular type are well demarcated and frequently encapsulated. Conversely, small HCCs of vaguely nodular type are poorly demarcated and retain the basic architecture of liver cirrhosis to a varying degree. Histologically, only about 20% of small HCCs of distinctly nodular type are uniformly composed of well-differentiated cancerous tissues. Another 20% consist of varying mixtures of well-differentiated and moderately differentiated cancerous tissues, and about 60% are already moderately differentiated. Tumor invasion into the portal vein and minute intrahepatic metastases in the vicinity of the tumor are found in 27% and 10%, respectively (Table 1). In contrast, many small HCCs up to about 1.5 cm in diameter are vaguely nodular and retain the basic architecture of the background cirrhotic liver in varying degrees. Most of these consist of the uniform distribution of well-differen-
entiated cancerous tissues with some cellular and structural atypia; the cancer cells show a replacing growth pattern at the tumor-nontumor boundary as if they are replacing the liver cell cords. In these well-differentiated early-stage HCCs, tumor-cell invasion into the portal tracts within the tumor is observed in varying degrees; this is called "stromal invasion" [Fig. 2A]. Stromal invasion is considered to be the most helpful morphological feature for differentiating well-differentiated HCC of vaguely nodular type from high-grade DNs. Well-differentiated HCCs in the early stage are characterized by increased cell density with nuclear/cytoplasmic ratio, increased cytoplasmic eosinophilia, and an irregular thin-trabecular pattern with a frequent pseudoglandular pattern. Diffuse fatty change is a prominent feature and is observed in about 40% of tumors about 1.5 cm in diameter; its frequency declines with increasing tumor size [Fig. 3]. Although the development mechanism of diffuse fatty change is still controversial, insufficient arterial blood supply to the tumor because of incomplete development of arterial tumor vessels (unpaired arteries) is suggested. In Japan, small, well-differentiated HCC of vaguely nodular type is designated "early hepatocellular carcinoma."

**Figure 1.** Gross findings of small HCC. (A) In distinctly nodular type, the tumor is 2 cm in diameter and encapsulated. (B) In vaguely nodular type, the tumor is 1.5 cm in diameter and the tumor boundary is indistinct (arrows; \( \uparrow \)).

**Table 1.** Morphologic Comparison of Distinctly Nodular HCC and Vaguely Nodular HCC Less Than 2 cm

|               | Vaguely Nodular (n=37) | Distinctly Nodular (n=69) |
|---------------|------------------------|---------------------------|
| Tumor size (mm) (mean ± SD) | 11.9 ± 3.3             | 16.0 ± 3.3                |
| Liver cirrhosis | 93%                    | 64%                       |
| Capsule       | 0%                     | 53%                       |
| Well-differentiated | 85%                    | 15%                       |
| Moderately differentiated | 0%                     | 58%                       |
| Portal vein invasion | 5%                     | 27%                       |
| Intrahepatic metastasis       | 0%                     | 10%                       |
| Angiography   | hypovascular           | hypervascular             |

**Figure 2.** Histologic features of well-differentiated HCC of vaguely nodular type. (A) The tumor consists of uniform distribution of well-differentiated cancerous tissue with some cellular and structural atypia. The portal tracts are retained in the tumor (arrow; \( \uparrow \)). (B) High-power view of the tumor-nontumor boundary (arrows; \( \uparrow \)). Well-differentiated HCC (left two-thirds of figure) is characterized by a marked increase in cellularity with an irregular thin-trabecular pattern and occasional pseudoglandular pattern, which increase staining affinity. The cancer cells proliferate as if they are replacing the liver cell cords of the noncancerous tissue.
Vascularization in Early HCC

In contrast imaging, small HCCs of distinctly nodular type and vaguely nodular type show different imaging patterns. The majority of small HCCs of distinctly nodular type are detected as hypervascular nodules by angiography and/or enhanced computed tomography. Conversely, many small HCCs of distinctly nodular type are hypovascular. There are 3 reasons for this hypovascularity. First, there is insufficient development of arterial tumor vessels (unpaired arteries) in the tumor. The number of arterial tumor vessels per square millimeter in tumors less than 1.5 cm in diameter is about two thirds of that of larger tumors and less than one third of tumors smaller than 1.5 cm (Fig. 4). Second, there is incomplete vascularization of the sinusoidlike blood spaces of the tumor. Although endothelial cells along the sinusoidal blood spaces of moderately differentiated HCCs are strongly positive to CD34, which is expressed in vascular endothelial cells, those along the sinusoidal blood spaces of early HCCs are negative or weakly positive. In addition, laminin, which is one of the constituents of the basement membrane of blood vessels, is weakly positive in early HCCs. These findings suggest incomplete vascularization of the sinusoidal blood spaces in early HCC as well as high-grade DNs.16–18 Third, the sinusoidal blood spaces and the sinusoids of the surrounding liver tissue are continuous at the tumor boundary. Because early HCCs have not yet become encapsulated, the sinusoidal blood spaces of the tumor are continuous with the sinusoids of the surrounding liver tissue, and a certain proportion of blood inflow to the tumor drains to the sinusoids of the surrounding liver tissue. In most small HCCs of distinctly nodular type, the arterial tumor vessels are well developed, sinusoidal blood spaces are well vascularized, and the tumors are encapsulated. Consequently,

Figure 3. Well-differentiated HCC of vaguely nodular type with fatty change. (A) The tumor was detected as a hyperechoic nodule during follow-up of a patient with HCV-related liver cirrhosis by ultrasonography. (B) Grossly, the tumor is 1.3 cm in diameter and is vaguely nodular. (C and D) Histologically, well-differentiated HCC is associated with diffuse fatty change.
many of them are detected as hypervascular tumors despite the small tumor size.

“Nodule-in-Nodule” Appearance

It is common to encounter small, well-differentiated HCC nodules containing a distinct minute nodule that consists of moderately differentiated HCC tissue in what is called “nodule-in-nodule” appearance (Fig. 5A). Nodule-in-nodule appearance can be considered a morphological expression of the progression of dedifferentiation of well-differentiated HCC. Nodule-in-nodule appearance is also easily visualized by ultrasonography. Specifically, when well-differentiated HCCs with fatty change contain less-differentiated HCC tissues without fatty change, those tumors are observed as hyperechoic nodules containing a distinct hypoechoic nodule. On clinical observation of these nodules, the hypoechoic nodule inside the hyperechoic nodule gradually increases in size along with the tumor; eventually, hyperechoic nodules are completely replaced by the hypoechoic nodule.

Confusion in Pathological Interpretation of Early HCC Between Japan and Western Countries

Regarding the pathological diagnosis of equivocal nodular lesions found in cirrhotic liver (especially in well-differentiated early-stage HCC), there is a discrepancy in interpretation between Japanese and Western pathologists. Specifically, many of the vaguely nodular HCCs of well-differentiated HCC tend to be diagnosed as high-grade DNs rather than HCC by Western pathologists. Conversely, many of the high-grade DNs diagnosed by Western pathologists are interpreted as well-differentiated HCC by Japanese pathologists. The presence of this discrepancy was confirmed at the International Consensus Meeting held in Kurume, Japan in April 2002. In that meeting, 30 resected cases of small nodular lesions up to 2 cm in diameter found in cirrhotic liver were examined by 8 Japanese and 9 Western pathologists who were expert in liver tumor pathology. Of 8 vaguely nodular tumors diagnosed as well-differentiated HCC by Japanese pathologists, 6 of the tumors were diagnosed as high-grade or low-grade DNs by many of the Western pathologists (Fig. 6A). At the end of the meeting, however, most Western pathologists agreed on a diagnosis of well-differentiated HCC.

Figure 4. Unpaired arteries in well-differentiated HCC of vaguely nodular type and moderately differentiated HCC. (A) Unpaired arteries are few in well-differentiated HCC. (B) There are many unpaired arteries in moderately differentiated HCC. (Immunostain of smooth muscle actin [α].)

Figure 5. A small HCC of the vaguely nodular type showing a “nodule-in-nodule” pattern. The vaguely nodular tumor is 2 cm in diameter and contains a distinct small nodule of 7 mm in diameter. Histologically, the outer tumor consists of well-differentiated HCC and the inner tumor (♀) is moderately differentiated HCC.
HCC on the basis of the recognition of stromal invasion in those tumors (Fig.6B). The reasons for the discrepancy between Japanese and Western pathologists can be explained by the following: for Western pathologists, most information comes from the study of advanced cirrhosis explanted at liver transplantation without detailed clinical information; for Japanese pathologists, most information comes from the examination of surgical and biopsy materials together with detailed clinical information that includes meticulous follow-up data on the clinical course of the nodular lesions.21–24

To resolve the diagnostic confusion concerning equivocal nodular lesions in the cirrhotic liver, it is necessary to promote the active exchange of clinicopathologic information between Japan and Western countries, not only among pathologists but also among clinicians.

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