Basic knowledge of interest

Multicentric occurrence of hepatocellular carcinoma: In terms of pathology study

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Abstract: The remarkable advances in diagnostic techniques and in the pathomorphologic study of minute hepatocellular carcinomas (HCCs) in the early stage indicate that many HCCs are multicentric in origin. Morphologically, combinations of HCC nodules and other nodules, such as adenomatous hyperplasia containing cancerous foci, well-differentiated HCC, or well-differentiated HCC containing moderate or poorly differentiated cancerous tissue are considered to originate and proliferate in situ. These combinations are considered to be HCC of synchronous multicentric origin. We found that, in HCC associated with liver cirrhosis, 6 of 74 consecutively resected HCCs (8.3%) and 4 of 8 autopsy cases (50%) satisfied the above criteria for multicentric origin. This discrepancy between surgical and autopsy cases can be explained thus: In surgical cases, morphologic examination is limited to only the vicinity of the main tumor and patients with multiple minute tumors HCC tend not to be sent to the operation table. Thus, the frequency seen in autopsy cases may reflect the true figures for multicentric origin. In 94 HCCs associated with chronic hepatitis, we found none showing coexistence of the above nodules that are suggestive of synchronous multicentric origin.

Key words: hepatocellular carcinoma, multicentric occurrence, synchronous multicentric occurrence, metachronous multicentric occurrence

Introduction

Whether hepatocellular carcinoma (HCC) is multicentric or unicentric in origin was a matter of controversy for many years. However, new morphologic information on early HCC and borderline lesions strongly suggests that many HCC could be of multicentric origin. In the past, multinodular HCCs in which each tumor nodule displayed a different histologic pattern tended to be considered of multicentric origin. On the other hand, some people supported the concept of unicentric origin, in the light of findings that most HCCs represent intrahepatic metastasis through portal vein tumor thrombus from a relatively early stage. However, as most morphologic studies were based on autopsy cases of advanced HCCs, conclusive evidence was not available.

In the past decade, however, extensive pathomorphologic studies have been carried out on a large number of surgically resected minute HCCs and biopsy specimens of early HCC. Further, the clinical courses of patients with liver cirrhosis and/or minute HCCs have been carefully monitored. The findings of these studies strongly suggest that many HCCs are synchronously or metachronously multicentric in origin.

Morphologic criteria for HCC of multicentric occurrence

Pathomorphologic studies of resected minute HCCs and biopsy materials from minute HCCs of the early stage show that: (i) the majority of minute HCCs (around 1 cm in diameter) are well-differentiated. (ii) With the increase of tumor size, the coexistence of less differentiated cancerous tissues is observed. (iii) In these HCCs, the area of less differentiated cancerous tissue is almost always surrounded by well-differentiated cancer and the well-differentiated cancer tissue diminishes in size with the increase of tumor size. The well-differentiated cancer is then completely replaced by moderately to poorly differentiated cancerous tissue. The dedifferentiation phenomenon, i.e., this replacement of well-differentiated cancerous tissues by less differentiated tissues, appears to be closely related to tumor proliferation in HCC. (iv) Adenomatous hyperplasia (AH) may be the precursor lesion of HCC, because AH frequently coexists with HCC and occa-
sionally contains foci of well-differentiated HCC within a nodule.\textsuperscript{7-9} (v) Some AHs develop into HCC during the course of clinical observation.\textsuperscript{10} (vi) In small HCC with indistinct margins, tumor invasion into the portal vein and intrahepatic metastasis are not found.\textsuperscript{11}

Based on these pathologic findings of early HCCs, morphologic criteria for multicentric HCCs have been proposed. The general rules for the clinical and pathological study of primary liver cancer, 3rd edition,\textsuperscript{12} define these criteria as follows: “AH containing cancerous foci”, “well-differentiated HCC”, and “well-differentiated HCC containing moderate or poorly differentiated cancerous tissues” are considered to have originated and proliferated in situ. When these combinations are present, the case is evaluated as HCC of synchronous multicentric origin. However, these criteria are not applicable to cases in which some HCCs of multicentric origin are rapidly dedifferentiated, presenting morphologic features of moderately or poorly differentiated tumors.

Multicentric HCCs are also classified as either synchronous or metachronous (in which the cancer nodules occur at different times). In the latter case, if newly developed HCCs satisfy the above mentioned criteria, they are evaluated as metachronously multicentric HCCs.

**Synchronous multicentric HCCs**

When non-cancerous liver tissues of surgically resected or autopsied HCCs contain cancerous lesions, such as well-differentiated cancer nodules (Fig. 1a,b) and/or well-differentiated cancerous nodules containing moderately differentiated cancerous tissues (Fig. 2a,b), which suggest the lesion has originated and is proliferating in situ, the cases are regarded as synchronous multicentric HCCs. Furthermore, in HCC with multiple nodules, if a needle biopsy of each tumor nodule discloses a well differentiated HCC, the nodules can be considered, clinically, as synchronous multicentric HCCs. The frequency of synchronous multicentric HCCs varies according to the presence or absence of liver cirrhosis, being extremely low in patients without liver cirrhosis.

**HCC associated with liver cirrhosis**

*Surgically resected and biopsy cases.* The authors' in a recent study, investigated non-cancerous liver tissues in 74 resected HCCs less than 2cm in diameter, obtained from patients with associated liver cirrhosis, finding minute nodules of well-differentiated HCCs in 6 cases. Therefore, 6 of the 74 cases (8.3%) satisfied the morphologic criteria for multicentric HCCs. This frequency could be a low estimation, for the following reasons: (i) Our observations were limited to only small areas in the vicinity of the main HCC nodule, and it is possible that other parts of the liver could have had similar lesions, which could not be depicted by diagnostic imagings. (ii) Patients who were assessed to have multiple nodules on preoperative examination tended not to be sent to the operation table. Therefore, the true frequency of synchronous multicentric occurrence in