Development and Growth Pattern of Small Hepatocellular Carcinomas in Woodchucks—Analysis of an Animal Model of Human Hepatocellular Carcinoma by Ultrasonography—

Junji SHIGA, Shin OHNISHI*, Michio IMAWARI*, Koshi YAMAMOTO**, Kaoru KOSHIMIZU**, and Nobuo SASAKI***

Department of Pathology, *Third Department of Internal Medicine, **Division of Animal Research, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, and ***Department of Veterinary Surgery, Faculty of Agriculture, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113, Japan

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Woodchucks are very useful animal models of human hepatocellular carcinoma. It is important to detect carcinomas in their early stage to study the pathogenesis of hepatocellular carcinoma. By ultrasonography (echogram) we found tumors less than 10 mm in diameter. Echographically all of the tumors except one were hypo-echoic in their early stages. One tumor showed a hyper-echoic pattern which grew very rapidly. Pathologically they were all well differentiated hepatocellular carcinoma and there were no differences between hypo- and hyper-echic tumors. When volumes of tumors were less than 10 cm$^3$ they grew very slowly but when tumors were larger than 10 cm$^3$ their volume increased very rapidly. The ultrasonographic patterns of large tumors were iso-echoic and mosaic, as in human hepatocellular carcinoma. — KEY WORDS : echogram, hepatocellular carcinoma, ultrasonography, woodchuck

The hepatitis virus of woodchucks (Marmota monax) is a hepadna virus like human hepatitis B virus (HBV) which causes human hepatocellular carcinoma (HCC). The woodchuck hepatitis virus (WHV) DNA has the same structure, molecular size and biological characteristics as HBV. It produces surface and core antigens like the human hepatitis B surface and core antigens [6]. WHV carriers, in contrast to non carriers, develope chronic hepatitis and then HCC in 3 to 5 years [4]. Progression of chronic hepatitis to liver cirrhosis, which occurs often in man, is evidently very rare in the woodchuck disease [4].

We have been engaged in studies using these animals as experimental models of human HCC since 1984 and succeeded in both indoor and outdoor breeding and care [2].

In our laboratory, ultrasonography is used routinely to detect HCC in its early stage. Already, 27 carrier animals have been repeatedly examined by this apparatus (EUB-22, 5 MHz, Histachi Medical Co. Tokyo). In 18 of these, HCC was found by this method and they were all surgically resected and confirmed histologically as HCC. In 6 of them the diameters of the tumors when first detected were less than 10 mm. The smallest tumor was 7 x 5 mm. The echopatterns of these 6 were all hypo-echoic except one which was hyper-echoic (Figs. 1 A and B).

Pathologically they had no tumor capsule and were all well differentiated HCC (Figs. 2 and 3). There was no morphological difference between hypo- and hyper-echoic tumors. The non-cancer part of the liver showed mild chronic hepatitis. Occasionally very small tumor nodules which could not be detected by ultra-
Fig. 1. Three echoic patterns of woodchuck HCC. A and B (arrows) are hypo- and hyper-echoic tumors respectively. The nodule surrounded by + in C shows a mosaic pattern.

Fig. 2. Resected tumor nodules. Nodules have no capsule.

Fig. 3. Microscopical appearance of HCC (H. E. staining, ×80).

Fig. 4. Advanced cancer sometimes shows dilated hepatic sinuses (H. E. staining, ×20).

Sonography were found by histological examination.

When tumors grew larger than 2 or 3 cm in diameter they had a so-called mosaic pattern as in human HCC (Fig. 1 C). Pathologically these large HCCs showed a more poorly differentiated pattern of cancer with a dilated sinus which formed sometimes so-called vascular lakes (Fig. 1). The echopattern coincided with these morphological changes.

The growth curves of the 6 small tumors less than 10 mm in diameter as they were first found are shown in Fig. 5. When the tumor volumes were less than 10 cm³ (tumor volumes were calculated as ellipsoid) they grew gradually and after that they did very rapidly. An
Fig. 5. Day 0 in this figure is the first day the tumors were found by echogram. The tumor of W6 was high-echoic. There are two curves of W1. One which redeveloped after operation was larger than 20 mm in diameter when first detected.

exception is the tumor which showed hyper-echoic pattern (W6 in Fig. 5). It grew rapidly from the beginning. From this tumor we succeeded in establishing a new cell line of woodchuck HCC as we previously reported [1].

Usually in the advanced stages of cancer, serum alkalinephosphatase (Alp) and gamma glutamyltranseptidase (γ-GTP) increase greatly [3], but all of our cases showed normal Alp and γ-GTP levels when the tumors were first found. In conclusion, ultrasonography is the best method to find tumors in the early stages of HCC.

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References
ウッドチャック初期肝細胞癌の発育と進展様式
——超音波画像診断による
ヒト肝細胞癌モデルの解析——

志賀淳治・大西 真*・井逹道夫**・山本孝史**

東京大学医学部附属病院病理部

*東京大学医学部第三内科
**東京大学医学部附属動物実験施設
***東京大学農学部獣医外科

ウッドチャック肝細胞癌はその発癌過程がヒト肝細胞癌によく似ており、ヒト肝細胞癌のよい動物モデルである。これまで27匹のウイルスキャリャーを繰り返し経時的に観察して、18匹に超音波画像診断方法により腫瘍を発見したが、このうち6匹では最大径1 cm以下の腫瘍であり、最小は7 mm × 5 mmであった。エコーパターンは1例以外は総てlow echoicで、1例のみがhigh echoicであった。エコーパターンによる病理解剖的な差はなく、いずれも良分化型の肝細胞癌であった。6例においてその発育過程を経過観察したが、腫瘍体積10 cm³以下では徐々に発育するが、それ以上では急激な体積の増加を示した。進行癌ではヒトと同じくいわゆるモザイクパターンを示した。