Long-term survival in a case of hepatocellular carcinoma.

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Abstract

A patient with an unresectable hepatocellular carcinoma (HCC) who survived without active treatment 3 years and 8 months after histological diagnosis is described. The size of the liver, which was already quite huge at the time of diagnosis, changed little during the entire clinical observation. However, 2 months before death, his condition deteriorated rapidly following gastrointestinal bleeding due to the direct invasion of the stomach by HCC. A critical reason for the unusually long-term survival of the patient may stem from the facts that a well-differentiated and bile-producing HCC was extent in most encapsulated-tumor tissues and that liver cirrhosis was not present.

KEYWORDS: hepatocellular carcinoma, long-term survival, well-differentiated type, hepatobiliary scintigraphy

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LONG-TERM SURVIVAL IN A CASE OF
HEPATOCELLULAR CARCINOMA

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The prognosis of hepatocellular carcinoma (HCC) is very poor and neither
an invasive nor non-invasive therapy effective against HCC has been established
yet. A few cases who had a long-term clinical course without any active treat-
ment against HCC have been previously reported (1-4). Recently we experienced
an unusual case of HCC with a protracted course who survived without aggres-
sive therapy for 3 years and 8 months following a definite histological diagnosis.
Clinical observation and autopsy findings of this patient are described, and the
characters of HCC associated with long-term survival are discussed.

CASE REPORT

A 56-year-old man was noted to have a large hepatomegaly during a rou-
tine physical examination in June 1977, at which time he was referred to the
nearest hospital for treatment of the liver. He had been well until then and had
no complaints, no family history of the liver disease, no drinking habit and no
history of blood transfusion. He was admitted to Okayama National Hospital
for further evaluation in July 1977. On physical examination, a firm liver was
palpable 12 cm below the xiphisternum, but neither ascites, jaundice, edema nor
dilatated abdominal veins was detected. No splenomegaly was found. Liver
function tests including serum alpha-fetoprotein (AFP) level were almost within
normal limits, and HBs antigen was negative. The patient was diagnosed as having primary hepatoma by $^{198}$Au-colloid liver scintigraphy and peritoneoscopy. An exploratory laparotomy revealed that the left lobe of the liver had multiple nodules, clearly demarcated from the remainder of the liver which had a smooth surface. No fluid was detected by puncturing the tumor. No other abnormalities such as metastasis of the tumor and ascites were noted. An incisional biopsy was made from the tumor located in the left lobe of the liver. The tissues was diagnosed histologically to be well-differentiated type of HCC. He was discharged several weeks later and was an outpatient of the hospital for 10 months. He received an anti-tumor agent, FT-207, at a daily dose of 600 mg during this period.

In February 1980, he was admitted to Okayama University Hospital for the purpose of following up on the HCC, although he had no complaints. On physical examination, the patient had a firm liver, of which the surface was nodular and the lower margin was located 13 cm under the xiphisternum. Several dilated veins were seen on the anterior abdominal wall, but splenomegaly and ascites were not observed. Liver function tests were almost within normal limits. Selective celiac angiography demonstrated two major tumor stains in the region of the right hepatic artery, 5 cm and 10 cm in diameter respectively, and multiple round smaller lesions suggestive of daughter tumor nodules located in both lobes. Transcathetherial administration of an anti-tumor agent was not performed because the tumors were so disseminated. He was discharged from the University Hospital a month later and his follow-up was continued in the outpatient clinic.

In the autumn of 1980, he first complained of general fatigue and slight dyspnea on exertion. Anemia and pretibial edema were manifested from that time. He was readmitted in January 1981. Palpable liver size had changed little over 3.5 years, and abnormality of the liver function tests was only moderate: serum GOT 96 U., AlPase 5.0 B.L.U. and ChEase 0.41 $\Delta$ pH. Serum AFP levels were low and HBs antigen was negative during the clinical course. Iron deficiency anemia probably due to gastrointestinal bleeding continued from the latter half of 1980. On physical examination, his abdominal wall with visible dilated veins was distended due to the large hepatomegaly palpable 14 cm along the median line. No ascites was noted. Conjunctiva was anemic and pitting edema of the lower extremities massive. His serum albumin concentration, ChEase activity and K$_{HCC}$ value fell below the respective normal values. Computerized abdominal tomography (CT) showed multinodular liver tumors, of which the capsule was clearly enhanced by administration of a contrast medium. On the hepatobiliary scintigram (Fig. 1), pooling of $^{99m}$Tc N-(2,6-diethylacetanilide)-iminodiacetic acid (EHIDA) was seen in the center portion of the liver where there was a defect in the $^{99m}$Tc Sn colloid and also where pooling of $^{67}$Ga citrate was noted. These results suggested that tumors had an ability to produce bile. The patient first had bloody vomit two weeks after readmission,
Fig. 1. Hepatobiliary scintigram (A) shows pooling of $^{99m}$Tc EHIDA in the center portion of the liver, where a defect of $^{99m}$Tc Sn colloid (B) and pooling of $^{67}$Ga citrate (C) are noted.

and thereafter hematemesis and melena continued. His condition deteriorated rapidly with the development of marked ascites and anasarca, and he died in March 1981. An autopsy was performed.

PATHOLOGICAL FINDINGS

A wedge-biopsy specimen of the left lobe of the liver obtained in 1977 shows a tumor of trabecular-sinusoidal structure without normal lobular anatomy (Fig. 2). The nucleus-cytoplasm ratio and chromatin volume are almost normal and the cytoplasm is very clear. Although atypism of tumor cells is not marked, polynuclear giant cells are scattered throughout. Bile pigments are also seen among tumor cells. From these observations, the section was diagnosed as being well-differentiated HCC.

The postmortem findings of the liver obtained 3 years and 8 months later
Fig. 2. A: Histological appearance of a wedge-biopsy liver specimen reveals a well-differentiated type of HCC. ×66. B: A giant cell. ×132. C: A bile plug. ×132. Hematoxylin and eosin stain.

Fig. 3. A: A cut surface of the autopsy liver shows multiple tumor nodules in both lobes. B: A schema of the photograph shows the distribution of Edmondson and Steiner's classification of HCC in each tumor nodule.

are as follows. The liver was 4200 g, and its firm surface was multinodular. Both lobes of the liver had various tumor nodules 5 mm to 5 cm in diameter (Fig. 3A). Color of the nodules was dark green, light or yellow brown. A thick capsule was observed, especially around greenish tumors, but seldom around other tumors. Fig. 3B shows the distribution of the histological grade of each tumor nodule according to Edmondson and Steiner's classification. Most portions of the tumors are occupied by grade II HCC, but regions showing grade IV was noticed in the right lobe of the liver. The non-tumor parenchyma of the remaining liver was compressed by tumor tissues, but no sign of liver
cirrhosis was observed.

The tumor directly invaded the lesser curvature of the stomach and formed ulcers which probably resulted in the gastrointestinal bleeding. Metastases were found in the lungs and the sternum. Bile pigment was seen microscopically in both metastatic tumors, and one tumor nodule in the sternum was green in color.

DISCUSSION

The prognosis of HCC with or without liver cirrhosis is very poor in general, and the survival period following definite diagnosis is usually only several months (1). HCC is often accompanied with liver cirrhosis (1), and this is one of the reasons why surgical reports of HCC cases with good prognosis are scanty. While non-surgical therapies such as chemotherapy, radiotherapy and transcatheter arterial embolization have been tried against inoperable HCC, survival has not been prolonged significantly. Edmondson (1), Lemmer (2), Hunt (3) and Eppstein (4) have already reported long-term survival in cases of HCC. Eleven cases of HCC who survived without active therapy more than 2 years following diagnosis have been reported in Japan (5-7). Our case is, however, the longest period of survival following pathological diagnosis of HCC reported to date.

The histological type of HCC in long surviving cases is mainly grade II of Edmondson and Steiner's classification (1). Liver cirrhosis and metastatic tumors are uncommon in cases with grade II, and their prognosis is fairly good. Our case also was diagnosed as well-differentiated type of HCC (grade II) even at the time of the autopsy. Hepatobiliary scintigram of the patient showed pooling of $^{99m}$Tc EHIDA which is an indication of bile production, a characteristic function of the liver (8). The morphologically and functionally well-differentiated HCC seems to be one of the major reasons why this patient remained alive for such a long period. The fact that liver cirrhosis did not accompany is probably another factor. Grades III and IV were seen in some of the tumor nodules, but the proportion of such HCC was very small. It may be postulated that clinical symptoms become manifest and the patient’s clinical course accelerates only after poorly differentiated tumors are generated and grow rapidly following a long latent period of grade II HCC (5). It is difficult, however, to judge when the enlargement of the patient’s liver occurred and how long the tumor persisted thereafter before the time of diagnosis.

The hepatoma tissues were well capsulated in this case. Okuda et al. stated that the fibrous capsule may be produced by the collapse of hepatocytes through compression, by condensation and collagenization of reticulin fibers and by inclusion of portal areas (9). Large capsules obviously contain large portal tracts since the celiac angiogram shows large distended arteries along the capsule. Capsules in our case were enhanced by use of contrast medium on the CT image. Growth seems to be slow because of the formation of a fibrous capsule around
the HCC, which in turn results in this frequency of metastasis being lowered once the capsule is made; the prognosis of HCC is improved.

In this case, serum AFP values were within normal limits throughout entire clinical course. It is thought that serum AFP value has a correlation with the histological grade of HCC; it remains low in cases with grades II and IV (10). In long-term survival HCC cases, including our case, histological types are well-differentiated and serum AFP levels seem to be low. Recently, HBs antigen has been suspected to be one of the most important factors in hepatocarcinogenesis. In our case, however, HBs antigen was not detected throughout the study.

REFERENCES