Capsular Formation Surrounding Hepatocellular Carcinoma

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In Japan, it is well known that most cases of hepatocellular carcinoma occur in the cirrhotic liver and this fact is regarded as a pathologic characteristic of hepatocellular carcinoma. Capsule formation surrounding the tumor is also a characteristic of hepatocellular carcinoma and it may be related to the developmental mode of hepatocellular carcinoma, to the clinical manifestation of symptoms and to the prognosis of the disease. The formation of the capsule can often be detected by means of modern imaging diagnostic procedures as well as sonography-guided or laparoscopy-guided needle biopsy of the liver.

This paper reports the results of an investigation on the incidence of capsular formation surrounding hepatocellular carcinoma and its clinicopathological considerations in hepatocellular carcinoma in its early stage occurring in liver cirrhosis.

(Key Words: Hepatocellular Carcinoma, Nodular Type, Capsular Formation, Massive Type, Diffuse Type, Diagnostic Imaging Procedure)

INTRODUCTION

Improvement of diagnostic procedures in modern hepatology on the basis of blood biochemical analyses and imaging diagnostics has enabled us to detect hepatocellular carcinoma in its early stage (8).

One of the pathological characteristics of hepatocellular carcinoma in Japan is that most cases of hepatocellular carcinoma occur in the cirrhotic liver (7, 8, 15, 18). Therefore, the occurrence of hepatocellular carcinoma must be given careful consideration in cases where liver cirrhosis can be diagnosed. To contribute to the early diagnosis of hepatocellular carcinoma occurring in patients with liver cirrhosis, a combination of sonography, scintigraphy, computed tomography and selective angiography, as well as sonography-guided or laparoscopy-guided needle biopsy of the liver was utilized regularly after initial diagnosis of liver cirrhosis. On the basis of the author's own experience, the effectiveness of the combination of such diagnostic procedures was stressed (8).

Another morphopathological characteristic of hepatocellular carcinoma is the capsular formation surrounding the tumor (4, 19), which is related to the development of hepatocellular carcinoma, to clinical manifestation of symptoms and to prognosis of the disease. The formation of the capsule can often be detected by means of modern imaging diagnostic procedures as well as sonography-guided or laparoscopy-guided needle biopsy of the liver.

To date, there have been very few reports on the incidence of capsular formation surrounding hepatocellular carcinoma, on the pathogenesis of the capsule and on clinical and prognostic considerations of the capsule from the clinical point of view in patients with hepatocellular carcinoma in its early stage occurring in liver cirrhosis.

This paper reports the results of an investigation on the incidence of capsular formation surrounding hepatocellular carcinoma and its clinicopathological considerations in hepatocellular carcinoma in its early stage occurring in cases of liver cirrhosis.

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MATERIALS AND METHODS
Among 345 patients with liver cirrhosis, in whom the diagnosis was made laparoscopically and bioptically in the past 7 years from 1977 to 1983 and clinical observations with our screening test for the detection of hepatocellular carcinoma in its early stage (8) had been regularly repeated up to the present, hepatocellular carcinoma developed in 37 patients, i.e., 11% of the 345 patients with liver cirrhosis, in whom alpha-fetoprotein in the serum, sonography, computed tomography, selective angiography and sonography-guided or laparoscopy-guided needle biopsy of the liver were utilized after initial diagnosis of liver cirrhosis. In particular, alpha-fetoprotein in the serum, sonography and scintigraphy were examined periodically after liver cirrhosis was first diagnosed.

Liver specimens, which were obtained from the liver by means of sonography-guided or laparoscopy-guided needle biopsy, were investigated histologically according to both the hematoxylin-eosin (H-E) and the Mallory-Azan staining methods.

Liver specimens were also obtained at the time of surgical operations and autopsy. In this way, capsular formation surrounding the hepatocellular carcinoma was investigated in these 37 patients with early stage hepatocellular carcinoma occurring in conjunction with liver cirrhosis.

In some of the patients with hepatocellular carcinoma together with liver cirrhosis, the staining of hepatocellular carcinoma with lipiodol, a contrast medium for X-ray examination, was performed at the time of angiography through the coeliac artery and the common hepatic artery.

When the tumor could be clearly revealed at the time of a surgical operation or autopsy, the correct size of the tumor and the capsular formation surrounding the tumor were investigated.

RESULTS
Among 345 patients with liver cirrhosis, in whom the diagnosis could be made laparoscopically and bioptically in the 7 years from 1977 to 1983 and the clinical course could be observed for at least 3 years after initial diagnosis, hepatocellular carcinoma occurred in 37 patients, in whom the screening test for hepatocellular carcinoma in its early stage was repeated regularly.

In 34 out of 37 cases, a tumor 3-4 cm in diameter could be detected and in these 34 cases, the tumor could be classified macroscopically as the nodular type of hepatocellular carcinoma. In two of the remaining three cases, three tumors of the nodular type could be detected in the borders between the right and left hepatic lobes. In the other case, a diffuse type of hepatocellular carcinoma was found.

The tumor occurred more predominantly in the right hepatic lobe than in the left lobe in a ratio of right to left to both hepatic lobes of 78: 14: 8. In addition, the ratio of macroscopic nodules of hepatocellular carcinoma, i.e., nodular to diffuse to massive type was 97: 3: 0.

In 32 out of 37 patients with hepatocellular carcinoma, scintigraphy revealed a space occupying lesion but showed no such lesion in the remaining five cases. Therefore, a diagnosis by scintigraphy was possible in 86% of patients with hepatocellular carcinoma. In spite of the diagnostic efficacy of scintigraphy, it was difficult to recognize capsular formation surrounding the tumor on the scintigram.

Fig. 1 is an example of a scintigram in a 70 year-old male patient (T.S.) with hepatocellular carcinoma in conjunction with liver cirrhosis. This scintigram showed a space occupying lesion in the right hepatic lobe and enlargement of the spleen. In spite of these findings, it was rather difficult to recognize any capsular formation surrounding the space occupying lesion.

In 31 out of 37 patients with hepatocellular carcinoma, sonography revealed an outline of a tumor in the hepatic lobe. In only one of the six remaining cases, sonography showed no demarcation of any tumor because this case was the diffuse type of hepatocellular carcinoma. Sonography was not performed in the remaining five cases. In cases, where scintigraphy demarcated the outline of the tumor, capsular formation surrounding the tumor could be traced, even if it appeared only faintly.

Fig. 2 shows a sonogram of the above-mentioned 70 year-old male patient (T.S.) obtained on the same day as scintigraphy was performed. Delineation around a tumor could be assumed from this sonogram but it was difficult.
Fig. 1  Scintigram of a 70 year-old male patient (T.S.) with hepatocellular carcinoma associated with liver cirrhosis on March 26, 1985

Fig. 2  Sonogram of a 70 year-old male patient (T.S.) with hepatocellular carcinoma on March 26, 1985
to trace any outline of capsular formation surrounding the tumor. Fig. 3 shows a sonogram taken 3 months later than that shown in Fig. 2 and on the 16th day after injection with lipiodol for selective angiography. As can be seen in Fig. 3, there was a marginal wall around the tumor and in inside of this wall, a few small partitions appeared by lipiodol staining.

In Fig. 4, a sonogram of a 55 year-old male patient (S.S.) with hepatocellular carcinoma in conjunction with liver cirrhosis is shown. In this sonogram, demarcation around the tumor could be inferred.

Generally speaking, sonography made it possible to infer hepatocellular carcinoma of the nodular type with demarcating capsular formation in 100% of the cases studied.

In 29 out of 37 patients with hepatocellular carcinoma, computed tomography could be performed and in 28 of the 29 cases studied, a low density area could be detected in a hepatic lobe, which correspond to hepatocellular carcinoma, i.e., it was possible to make a diagnosis by computed tomography in 97% of the cases studied. At the same time, a thin demarcating membranous structure around the hepatocellular carcinoma could be faintly inferred which might be suggestive of capsular formation surrounding the carcinoma. Fig. 5 shows a computed tomogram of the above-mentioned 70 year-old male patient and Fig. 6 a computed tomogram in the above-mentioned 55 year-old male patient.

The thin demarcating membranous structure became a little more conspicuous after injection of contrast medium into the liver for an X-ray examination (Fig. 7 and 8).

In 35 out of 37 patients with hepatocellular carcinoma in conjunction with liver cirrhosis, selective angiography through the coeliac artery and common hepatic artery made possible a correct diagnosis and in the remaining two patients, this diagnostic procedure failed, i.e., angiographic diagnosis was possible in 95% of the cases studied. With this diagnostic procedure, hepatocellular carcinoma of nodular type could be delineated clearly from the surrounding non-carcinomatous liver tissue. Therefore, capsular formation surrounding the tumor could be conjectured, even if no membranous structure surrounding the tumor was recognized.

In Fig. 9, a selective angiogram in the arterial phase of the 55 year-old male patient is shown. Fig. 10 is a selective angiogram in the arterial phase of the 70 year-old male patient and in the middle of the right group of arterial branches, the main tumor could be assumed. Simultaneously, lipiodol was injected through a cannula for angiography and in Fig. 11, an outline of the hepatocellular carcinoma in the right lobe seen immediately after injection is shown. A few partitions within the outline of the tumor could be inferred.

If lipiodol was injected through a cannula at the time of selective angiography and localized accumulation of the lipiodol could be observed, demarcation with a faint thin membranous structure appeared surrounding the tumor. In this case, several partitions were seen. It was also helpful to observe the site of lipiodol accumulation with the lapse of time after injection. Fig. 12 shows the accumulation of lipiodol in the right hepatic lobe in computed tomography on the 8th day after injection.

The most decisive recognition of capsular formation surrounding the tumor, however, can be made on the basis of histological findings at the site of the hepatocellular carcinoma and its surroundings. Therefore, laparoscopy-guided or sonography-guided needle biopsy of the liver was performed and in the 36 patients with hepatocellular carcinoma of the nodular type, liver specimens sufficient for histological examination could be obtained. Liver specimens could also be obtained from the remaining patient with hepatocellular carcinoma of the diffuse type but it was impossible to recognize capsule formation.

In nine out of 36 patients with hepatocellular carcinoma of the nodular type, capsular formation around the tumor could be detected and in the remaining 27 patients, capsular formation could be recognized on the basis of histological examinations of liver specimens removed at the time of surgical operations or autopsy.

Fig. 13-a and b shows macroscopic findings of capsulated hepatocellular carcinoma with a nodular configuration 3 cm in diameter in the resected right hepatic lobe in the above-mentioned 55 year-old male patient. Histological examination of the capsule revealed that it consisted principally of collagen fibers. In this
Fig. 3  Sonogram of a 70 year-old male patient (T.S.) on June 26, 1985, taken 3 months after that shown in Fig. 2 and on the 16th day after selective angiography with Lipiodol injection.

Fig. 4  Sonogram of a 55 year-old male patient (S.S.) with hepatocellular carcinoma in conjunction with liver cirrhosis
Fig. 5 Computed tomogram of the above-mentioned 70 year-old male patient (T.S.) on April 4, 1985.

Fig. 6 Computed tomogram of the above-mentioned 55 year-old male patient (S.S.).
Fig. 7  Computed tomogram with contrast enhancement after injection of contrast medium for X-ray examination of the above-mentioned 70 year-old male patient (T.S.) on April 4, 1985.

Fig. 8  Computed tomogram with contrast enhancement after injection of contrast medium for X-ray examination of the above-mentioned 55 year-old male patient (S.S.).
Fig. 9  Selective angiogram in the arterial phase of the above-mentioned 55 year-old male patient (S.S.).

Fig. 10  Selective angiogram in the arterial phase of the above-mentioned 70 year-old male patient (T.S.) on June 10, 1985.
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Fig. 11 Selective angiogram immediately after simultaneous injection with Lipiodol of the above-mentioned 70 year-old patient (T.S.) on June 10, 1985.

Fig. 12 Computed tomogram of the 70 year-old male patient (T.S.) on June 18, 1985, i.e., 8 days after Lipiodol injection at the time of selective angiography.
Fig. 13-a  Capsulated hepatocellular carcinoma with a nodular configuration 3 cm in diameter in the resected right hepatic lobe of the 55 year-old male patient (S.S.).

Fig. 13-b  Capsulated hepatocellular carcinoma with a nodular configuration 3 cm in diameter in the resected right hepatic lobe of the 55 year-old male patient (S.S.) after fixation in 40% formalin solution.
Fig. 14-a  Histological findings of the biopsied liver of the 70 year-old patient (T.S.) (HE stain, 100×).

Fig. 14-b  Histological findings of the biopsied liver of the 70 year-old patient (T.S.) (Mallory-Azan stain, 100×).
patient, a surgical operation was performed successfully and he is alive and well more than 1 year after the operation.

Histological findings of the liver by means of a needle biopsy in the 70 year-old patient showed the formation of a partition within the tumor, which divided the area of the hepatocellular carcinoma of grade 2 according to Edmondson-Steiner's classification (4) from the area of necrosis (Fig. 14-a and b). Fig. 14-a shows histological findings according to the hematoxylin-eosin staining method and Fig. 14-b by the Mallory-Azan staining method. These findings were suggestive of the pathogenetic process of capsular formation surrounding hepatocellular carcinoma and the partition in the carcinoma.

DISCUSSION

One of the pathological characteristics of hepatocellular carcinoma in Japan is that most cases occur in the cirrhotic liver (7, 8, 15, 18). Therefore, the occurrence of hepatocellular carcinoma must be given careful consideration in cases where liver cirrhosis can be diagnosed. To contribute to early diagnosis of hepatocellular carcinoma in patients with liver cirrhosis, a combination of estimation of the serum alphafetoprotein level and various imaging diagnostic procedures was utilized as a screening test. In the 7 years from 1977 to 1983, diagnosis of liver cirrhosis was made laparoscopically and biopically in 345 patients in whom the clinical course could be observed for at least 1 year after initial diagnosis. Among these 345 patients, hepatocellular carcinoma occurred in 37 patients, i.e., 11% of the patients with liver cirrhosis in whom the author's screening was repeated regularly.

Another morphologic characteristic of hepatocellular carcinoma is capsular formation surrounding the tumor (19). On the basis of examinations of these 37 patients with hepatocellular carcinoma in conjunction with liver cirrhosis, capsule formation surrounding the tumor and its clinical and pathological significance in hepatocellular carcinoma must be taken into consideration because very few investigations of hepatocellular carcinoma in its early stage have been reported to date.

In 34 out of 37 patients with hepatocellular carcinoma in conjunction with liver cirrhosis, a tumor 3-4 cm in diameter could be detected in a hepatic lobe and in two of the remaining three cases, three tumors of 2-3 cm in diameter were seen in the borders between the right and left hepatic lobes. In these cases, hepatocellular carcinoma could be classified macroscopically into the nodular form. In the other case, a diffuse form of hepatocellular carcinoma was found. Therefore, the nodular form of hepatocellular carcinoma was observed in 36 out of 37 patients, i.e., in 97% of the patients in whom tumors 2-4 cm in diameter could be detected. Therefore, it can be said that hepatocellular carcinoma in conjunction with liver cirrhosis could be classified into the nodular form in 97% of the patients with hepatocellular carcinoma in its early stage if the tumor was in a range of 2 to 4 cm in diameter. In the remaining case of the diffuse form, no delineation of a tumor was recognizable and no imaging diagnostic procedure could clarify the hepatocellular carcinoma but needle biopsy of the liver alone was useful to diagnose the disease effectively. Hitherto the reported incidences of each macroscopic form of hepatocellular carcinoma (Table 1) (6, 11, 20) apparently differed from

<table>
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the author's observations. These difference seemed to originate from different conditions of the disease. The previously reported cases (6, 11, 20) belonged to groups of rather advanced hepatocellular carcinoma so that in the autopsied liver in most cases and in the surgically resected liver in some cases, pathological findings of hepatocellular carcinoma were investigated. Recently, Kojiri et al. (14) pointed out that capsular formation surrounding hepatocellular carcinoma could be detected in 21 out of 23 autopsied patients and in 10 out of 11 partially resected patients with small hepatocellular carcinomas of the nodular form less than 2 cm in diameter. These facts were consistent with the author's observations in this study. To date, the tendency to detect small hepatocellular carcinoma in Japan seems to be intensified because transcatheter embolization therapy for hepatocellular carcinoma in its early stage is now applied mostly to patients with the disease if the tumor is solitary and less than 3-4 cm in diameter (1, 2, 14, 16, 17). It has now become common in Japan to detect hepatocellular carcinoma less than 3-4 cm in diameter in patients with liver cirrhosis in whom the clinical course after initial diagnosis of liver cirrhosis has been observed for at least one year.

Capsular formation surrounding hepatocellular carcinoma, i.e., capsulated hepatocellular carcinoma, which might be either a partially capsulated tumor or totally capsulated tumor, is closely related to the nodular form of hepatocellular carcinoma. Therefore, capsular formation in the nodular form of hepatocellular carcinoma must be investigated. In patients with the nodular form, which could be detected due to modern diagnostic imaging procedures, the possibility of detecting capsular formation around the tumor using these diagnostic imaging procedures should be evaluated. In particular, computed tomography, sonography and selective angiography with simultaneously injected lipiodol should prove very reliable, if skill is attained in these diagnostic procedures (5). These diagnostic imaging findings must be compared with histological changes in the liver including both the site of hepatocellular carcinoma and the region of the non-pathological liver surrounding the hepatocellular carcinoma. For this purpose, specimens had to be taken from the liver using laparoscopy-guided or sonography-guided needle biopsy or at the time of surgical operations or autopsy. In the nodular form of hepatocellular carcinoma 2-4 cm in diameter, partial or total capsular formation surrounding the tumor might be inferred. In this investigation, capsular formation could be surmised in all cases of the nodular form of hepatocellular carcinoma and these findings were supported by histological examinations. It has already been reported that totally capsulated hepatocellular carcinoma accounted for 57% of 129 patients with hepatocellular carcinoma and partially capsulated ones for 17.3% (11). As mentioned above, these 129 patients had advanced hepatocellular carcinoma, while in the author's 57 cases, hepatocellular carcinoma occurred in the clinical course after initial diagnosis of liver cirrhosis, and hepatocellular carcinoma of the nodular form could be diagnosed in 36 of these patients. On the basis of the author's observations, it must be stressed that in the nodular form of hepatocellular carcinoma 2-4 cm in diameter, either partial or total capsular formation surrounding the tumor was recognized.

In hepatocellular carcinoma with a nodular configuration, the neoplastic foci are so small that no modern diagnostic procedure can reveal the disease clinically. In practice, a tumor more than 2 cm in diameter can usually be detected by diagnostic imaging procedures (1, 2, 8, 14, 16, 17). Therefore, a tumor more than 2 cm in diameter can be detected by technical experts in clinical practice and therefore, capsular formation surrounding the tumor and its clinical significance comes into question.

Initially, neoplasms bulge beneath Glisson's capsule in highly advanced cirrhosis of the liver (5) and they coalesce into a tumor with a nodular configuration 2 cm in diameter. The tumor can be detected clinically after a series of scintigraphy, sonography, computed tomography and selective angiography, repeated as a screening test for hepatocellular carcinoma occurring in conjunction with liver cirrhosis. In the latent stage of neoplastic bulging, the neoplastic nature of the process may not be apparent on gross inspection but very small neoplastic foci may be scattered in highly advanced cirrhosis. Generally speaking, the neoplastic foci coalesced and emerged into a small tumor in a fa-
vored site of development within the liver (10). Carcinogenic factors were not yet clear (9).

These neoplasms are often friable and may be hemorrhagic. In the present investigation, histological examination by needle biopsy of the liver revealed necrosis in part of the carcinoma cells, which was separated from the surrounding tumor by a partition. Degenerative and necrotic changes of the cells due to expansive compression of the borders of the tumor may bring about capsular formation around small hepatocellular carcinomas as a pathogenic factor. Histological findings by liver biopsy included such fibrotic processes. In the same way, partition formation within the tumor could be also recognized. However, the contributing factors which lead to degeneration and necrosis of hepatic carcinoma cells are still not clear.

Fever with leucytosis of the peripheral blood is a characteristic clinical manifestation in patients with hepatocellular carcinoma. On the basis of the present study, it has become clear that these clinical manifestations seemed to be related to the histological findings of necrosis of hepatic carcinoma cells including inflammatory changes.

To date, 33 out of 37 patients with hepatocellular carcinoma in its early stage, in whom the carcinoma occurred in conjunction with liver cirrhosis, died mostly of complications such as hepatic insufficiency and gastrointestinal bleeding. The most noteworthy cause of death was bleeding into the abdominal cavity following rupture of the capsulated hepatocellular carcinoma. Ten out of these 33 patients died from bleeding following rupture of the capsulated hepatocellular carcinoma. In such cases, intraarterial administration of anticancer drugs should be considered as a causative factor of bleeding because such therapeutic procedures were performed in these patients. It must be carefully considered whether the anticancer drugs themselves or changes in pressure within the tumor at the time of intraarterial injection through the coeliac artery or common hepatic artery might be connected with rupture of the capsule surrounding the carcinoma.

Lipiodol injection through the coeliac artery and the common hepatic artery at the time of selective angiography is a very reliable procedure for diagnosis of small hepatocellular carcinomas with a nodular configuration (5) and also for recognition of capsular formation surrounding the hepatocellular carcinoma. However, patients in whom lipiodol injection was performed became feverish after the procedure and necrosis of hepatic carcinoma cells within part of the tumor was seen, if sonography-guided needle biopsy of the liver was performed. In such cases, it is also difficult to clarify the part played by lipiodol. In any case, necrosis of carcinoma cells including inflammatory changes and congestion in part of the hepatocellular carcinoma may bring about expansion of the tumor and capsular formation around the tumor. At the same time, such inflammatory process also causes partition formation within the tumor. However, the contributing factors to the inflammatory process remained to be elucidated. Lipiodol injection through the coeliac artery and the common hepatic artery has been attempted as anticancer therapy for small hepatocellular carcinoma (12, 13).

In conclusion, it can be said that capsular formation surrounding a small hepatocellular carcinoma 2-4 cm in diameter can be recognized in patients with liver cirrhosis due to modern diagnostic imaging procedures. Capsular formation is a characteristic pathological finding of hepatocellular carcinoma with a nodular configuration in Japan.

REFERENCES