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<td>Author(s)</td>
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Spontaneous Rupture of Hepatocellular Carcinoma

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ABSTRACT: Of 105 patients of hepatocellular carcinoma (HCC) treated during 1970-1988, twelve patients had spontaneous rupture of carcinomatous nodules. 1) Of previous 6 cases, five were treated by conventional surgical procedures such as packing and suture, and all died. One case underwent right lobectomy following gauze pack and lived for 15 months. 2) The recent 6 cases underwent emergency transcatheter arterial embolization (TAE) and two died of hepatic failure due to severe cirrhosis. The other 4 cases had successful control of bleeding which allowed further treatment of HCC; hepatectomy in 3 and repeated TAE in one. 3) All cases had pre-cirrhosis or cirrhosis. Pathologically, ruptured tumors expansively growing with capsule invasion of cancer cells, and portal tumor thrombus were recognized in resected or autopsy specimens. DNA aneuploid HCC on flow cytometric DNA analysis were found in 4 out of 5 cases.

In conclusion, hepatic resection following embolization, when possible, would seem to be rational treatment for spontaneous rupture of HCC, although the prognosis is still extremely poor despite successful control of bleeding.

INTRODUCTION

Spontaneous rupture of hepatocellular carcinoma (HCC) is not a rare event in Japan, although it is relatively uncommon or rarely recognized in Europe and the United States. Most series dealing with spontaneous rupture of HCC from Asia or Africa have been reported the incidence at 4-14.5%. Spontaneous rupture of HCC is emergency complication which is difficult to treat, and the prognosis is extremely poor without proper management. However, recent advanced imaging modalities such as ultrasonography (US) or computed tomography (CT) make it possible to detect ruptured HCC. This had led to the significant improvement in the management of spontaneous
rupture of HCC. Transcatheter arterial embolization (TAE) is now being used not only for diagnostic purposes but also in the treatment of ruptured HCC.5-9)

The purpose of this article is to review our experience with spontaneous rupture of HCC, in appraisal of control of hemorrhage and therapy of HCC, and to investigate the pathological features of the ruptured HCC which might affect the patient’s survival.

**MATERIALS AND METHODS**

From January 1970 to December 1988, 105 patients with HCC were treated at our hospital. Twelve patients of this series who had spontaneous rupture of HCC were reviewed. The current series of rupture of HCC represented a sequel to the previous series with 6 patients reported from our department by authors covering the period from 1970 to 1977.10) Data from the previous series were presented to analyze some changing concepts in comparison with 6 patients in the recent series form 1978 to 1988, in which most patients were diagnosed by US or CT. In order to study the nature of ruptured tumor, pathological features of 7 ruptured tumors taken from operation and/or autopsy were investigated, and cellular DNA content was also measured in paraffin-embedded materials from 5 cases of HCC available by flow cytometry (FCM) according to Schutte’s method.11)

The profile of 12 patients with ruptured HCC is listed in Table 1. There were 11 men and one woman ranging in age from 36 to 68 years with mean age of 52 years. Chronic liver disease was observed in all cases.

Recent six patients had been known to be associated with HCC before the onset of rupture of HCC (Case 1-6), and the other 6 in the previous series (Case 7-12) admitted with sudden onset of abdominal pain, and underwent emergency laparotomy to find ruptured HCC. Mode of ruptured HCC was subcapsular rupture in 3 cases (Case No. 4, 5, 6) and intraperitoneal bleeding in 9. Abdominal paracentesis was performed in 7 cases to confirm the presence of hemoperitoneum. US and CT prior to angiography were done for the recent 6 cases (Fig. 1, 2). Emergency hepatic angiography was performed for 6 cases, and the bleeding sites of hepatic tumors were identified in 3 cases (Fig. 3). In the other 3 cases, however, the extravasation of contrast material was not shown but typical hypervascular tumor were noted.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr) /Sex</th>
<th>Gross Appearance</th>
<th>Extravasation on Angiography</th>
<th>Management</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57/M</td>
<td>Nodular +</td>
<td>TAE</td>
<td>died</td>
<td>7 days</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>Nodular +</td>
<td>TAE</td>
<td>died</td>
<td>2 days</td>
</tr>
<tr>
<td>3</td>
<td>49/M</td>
<td>Nodular +</td>
<td>TAE</td>
<td>alive</td>
<td>18 mon.</td>
</tr>
<tr>
<td>4</td>
<td>43/M</td>
<td>Massive -</td>
<td>TAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>62/M</td>
<td>Massive -</td>
<td>Left lobectomy</td>
<td>24 mon.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>58/M</td>
<td>Massive -</td>
<td>TAE</td>
<td>died</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>43/M</td>
<td>Nodular -</td>
<td>Right lobectomy</td>
<td>1 mon.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>66/M</td>
<td>Nodular NE</td>
<td>Right lobectomy</td>
<td>died</td>
<td>15 mon.</td>
</tr>
<tr>
<td>9</td>
<td>36/M</td>
<td>Nodular NE</td>
<td>Packing</td>
<td>died</td>
<td>14 days</td>
</tr>
<tr>
<td>10</td>
<td>39/M</td>
<td>Massive -</td>
<td>Packing</td>
<td>died</td>
<td>8 days</td>
</tr>
<tr>
<td>11</td>
<td>48/M</td>
<td>Nodular NE</td>
<td>Packing</td>
<td>died</td>
<td>12 days</td>
</tr>
<tr>
<td>12</td>
<td>67/M</td>
<td>Nodular -</td>
<td>Packing</td>
<td>died</td>
<td>15 days</td>
</tr>
</tbody>
</table>

NE : not examined
Fig. 1. Emergency ultrasonography in Case 6 showing 4.7×3.5 cm hypoechoic lesion with an abrupt of peripheral rim (arrow) which suggested ruptured HCC.

Fig. 2. CT imaging of Case 4 demonstrating subcapsular rupture of HCC in left lobe.

TREATMENTS AND RESULTS

Recent 6 patients underwent emergency TAE using stainless-steel coil. A mixture of Gelform, 20 mg of mitomycin C (MMC) and contrast material was administered into the hepatic artery of one case (Case No. 3). Three patients with subcapsular rupture were managed by lipiodolization suspended with 20 mg of MMC or adriamycin. Celiac angiography after embolization revealed the disappearance of extravasation and occlusion of the tumor vessels in all cases. Two patients who had severe cirrhosis and multiple intrahepatic metastases died 2 and 7 days after TAE because of hepatic failure and gastric bleeding following DIC. One patient (Case 2) who had two tumors in right lobe was repeatedly treated by TAE only (Fig. 4), and is still alive 18 months after initial TAE.

Fig. 3. Selective hepatic angiogram in Case 3 demonstrating a solitary hypervascular tumor with irregular and tortuous vessels and extravasation of contrast media from anterior branches of right hepatic artery (arrow).

Fig. 4. CT imaging 6 months after embolization in the same case as figure 3 showing a high density area with retension of lipiodol (arrow) and markedly reducing in tumor size.
Three patients with subcapsular rupture from solitary tumor underwent hepatic resection 14 days, 25 days and 15 months later, respectively. One patient with right lobectomy (Case 6) developed progressive jaundice and had uneventful course despite treatment of plasmaphoresis. The patient with subsegmentectomy (case 5) lived for 9 months, but finally died of recurrence of the tumor. The third patient with left lobectomy (Case 4) was alive 2 years after operation without any recurrence.

In the previous series, one patient (Case 7) was referred to our hospital with guaze packing because of ruptured HCC from right lobe in a hospital, and right lobectomy was done 21 days after initial surgery. He died of recurrence 15 months after second surgery. The other 4 patients underwent conventional procedure such as oxcel, gelform or omental packing, resulted in early death.

Pathologic features

Macroscopic types of rupture of HCC on angiogram and/or operative findings were 8 cases in nodular and 4 in massive, but none was diffuse (Table 1).

Pathologic findings and tumor ploidy of 7 ruptured tumors taken from operation and autopsy were summarized in Table 2. All cases had chronic liver disease; precirrhosis, 2 case; and liver cirrhosis, 5 cases. The maximum diameter of ruptured tumors ranged from 3.0 cm to 10.5cm.

Grossly, these tumors were firmly encapsulated by fibrous tissues, which demonstrated expansive growth, and rupture was observed at the surface of the tumor (Fig. 5).

Histologic type according to Edmondson’s classification was grade II in 4 cases and grade III in 3. Invasion of cancer cells extending through capsule and the presence of tumor thrombus were microscopically observed in 6 cases. In one case (Case 6), most of the tumor had been necrotic by TAE, although viable tumor cells were found in the periphery of tumor capsule.

Tumor ploidy patterns on flow cytometric DNA analysis were aneuploid in 4 cases and diploid in one.

**DISCUSSION**

The clinical features of ruptured HCC are sudden onset of severe abdominal pain, shock,

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Size (cm)</th>
<th>Histol.</th>
<th>fc</th>
<th>fc-inf</th>
<th>vp</th>
<th>DNA Index</th>
<th>Existing liver disease</th>
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<tbody>
<tr>
<td>1*</td>
<td>57/M</td>
<td>3.0</td>
<td>III</td>
<td>+</td>
<td>++</td>
<td>2</td>
<td>NE</td>
<td>LC</td>
</tr>
<tr>
<td>4</td>
<td>68/M</td>
<td>10.5</td>
<td>II</td>
<td>+</td>
<td>+</td>
<td>1</td>
<td>2.07 (Ap)</td>
<td>PC</td>
</tr>
<tr>
<td>5</td>
<td>62/M</td>
<td>7.8</td>
<td>III</td>
<td>+</td>
<td>+</td>
<td>1</td>
<td>1.55 (Ap)</td>
<td>PC</td>
</tr>
<tr>
<td>6</td>
<td>58/M</td>
<td>4.7</td>
<td>II</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>NE</td>
<td>LC</td>
</tr>
<tr>
<td>7</td>
<td>43/M</td>
<td>3.5</td>
<td>II</td>
<td>+</td>
<td>++</td>
<td>2</td>
<td>1.81 (Ap)</td>
<td>LC</td>
</tr>
<tr>
<td>8</td>
<td>66/M</td>
<td>6.0</td>
<td>II</td>
<td>+</td>
<td>++</td>
<td>2</td>
<td>2.17 (Ap)</td>
<td>LC</td>
</tr>
<tr>
<td>11*</td>
<td>48/M</td>
<td>6.5</td>
<td>III</td>
<td>+</td>
<td>++</td>
<td>2</td>
<td>1.0 (Dp)</td>
<td>LC</td>
</tr>
</tbody>
</table>

* : Autopsy case ; fc : capsule formation ; fc-inf : capsule invasion of cancer cell ; vp : portal tumor thrombus ; (Ap) : aneuploidy ; (Dp) : diploidy ; PC : Precirrhosis ; LC : liver cirrhosis
and presence of blood in the peritoneal cavity. In the previous series, diagnosis have been made by the history of HCC, detection of the bloody ascites by abdominal paracentesis, and the hypervascular tumors and the extravasation of the contrast material on hepatic angiogram\(^2\), \(^4\), \(^10\), \(^12\). In the patients with acute abdominal pain without a history of HCC, it is difficult to diagnose accurately the spontaneous rupture of HCC\(^2\), \(^4\), \(^12\). In our 3 patients, laparotomy was due because of uncertain diagnosis and suspicion of peritonitis. However, in our recent 6 cases, US, CT and angiography proved to be most useful in the diagnosis of ruptured HCC. Of these diagnostic modalities available, US could evaluate pathological features of the tumor and its location\(^13\). Ruptured HCC were hypoechoic with some strong central echogenicity, reflecting the pathological features such as partial abruptly capsule and tumor parenchyma with necrosis.

Arteriography may provide useful information on the vascular supply of the tumor with bleeding vessels, and also can be utilized for the therapy of TAE for active sources of hemorrhage, although the incidence of extravasation of contrast material on angiography has been reported to range from 24% to 35.7% of ruptured HCC\(^5\)–\(^9\).

Successful control of bleeding by emergency embolization of the hepatic artery and a longer survival was achieved in 4 out of 6 cases. This allowed further treatment of the HCC, as compared with conventional surgical procedure such as suture and packing which failed to control hemorrhage in most cases due to friability or necrosis of the tumor. Generally, it has been reported that the mortality rate of those who underwent conventional surgical procedures including hepatic arterial ligation was 52.9%–90%\(^4\), \(^5\), \(^14\). Our current series suggests that TAE should be a useful therapeutic modality for spontaneous rupture of HCC even in the patient with advanced stage of HCC, and that surgery should be performed only when the embolization fails to control the bleeding.

There are many reports of TAE for reducing the tumors of HCC. However, embolization had substantially no effect on daughter nodules or tumor thrombi within the portal vein, which seems to improve certain limitations on the application of this therapy\(^15\)–\(^17\). Hepatic resection followed by TAE, when possible, would seem to be the rational treatment for spontaneous rupture of HCC.

Several factors contributing to rupture of HCC have been pointed out\(^5\), \(^18\): pathologically, 1) encapsulated tumor, 2) capsule invasion of cancer cells, 3) portal tumor thrombus, 4) tumor size, and physiologically, 1) neovascularization, 2) increased intrahepatic shunting, 3) obstruction of branches of the hepatic vein draining the tumor bearing area, 4) portal hypertension due to preexisting cirrhosis.

In the present series, the rupture occurred almost exclusively in cases with associated cirrhosis, and several pathologic features contributing to rupture were observed in most cases. But two cases had the ruptured tumor smaller than 4 cm in size. It was considered that the tumor expansively growing in coexisting cirrhosis was particularly prone to rupture even in small size, and that the physiological factors would seems to play important roles in the pathogenesis of the spontaneous rupture.

The prognosis of the patient with rupture of HCC is still extremely poor despite successful control of the bleeding. It has been shown that numerous clinical and histological parameters have prognostic significance in HCC\(^19\), \(^20\). The important factors affecting the patient’s survival have been the presence or absence of cirrhosis and stage of the disease\(^21\). Recently, many reports have suggested that the DNA content of the tumor was important for the prognosis, but a few have been studied on HCC\(^22\)–\(^24\). We recognized DNA aneuploid pattern on flow cytometric DNA analysis in 4 out of 5 ruptured specimens. The aneuploid tumor may lead to rapid dissemination of the disease and patient death within a short period of time as has been noted for some other human tumors. But the results of this report must be confirmed by additional data based on a large group of patients.
REFERENCES


