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A Case of Hepatocellular Carcinoma With Sarcotomatous Change Arising After Repeated Transcatheter Arterial Embolization

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We report a case involving a moderately differentiated hepatocellular carcinoma (HCC) developing into an HCC with sarcomatous change after repeated transcatheter arterial embolization (TAE). In a 56-year-old patient with an alcoholic hepatitis, multiple HCC lesions were detected by abdominal ultrasonography. A dynamic arterial-phase computed tomography (CT) demonstrated a moderately differentiated HCC with a 2cm-diameter tumor in segment II, a 1 cm-diameter tumor in segment VI, and two 6mm-diameter tumors in segment VII. TAE was performed on this patient three times. After this therapy, the HCC in segment II was completely healed, but a new nodule developed in segment VI 22 months after the first TAE procedure, and the HCC rapidly grew, involving adjoining organs. Eventually, the patient died as a result of failure of liver function and multiple organs.

Autopsy findings showed a massive hepatic necrotic hemorrhage with a tumor measuring 14 cm involving segment VI with massive invasion into the peritoneum. Several nodules were scattered through segments IV, V, and VIII. Lymph node metastases were observed in the paragastric, retroperitoneal, and lung hilar regions. Histologically, the massive hepatic tumor consisted of spindle cells or pleomorphic cells compatible with sarcoma. Other nodules were diffusely involved in the necrosis and partially remained as well to moderately differentiated trabecular HCC. There was no transitional line between the HCC and sarcomatous spindle cells. An immunohistochemical study showed that the sarcomatoid cells were positively stained for smooth muscle actine (SMA), CD(117) (c-KIT), and anti-melanosoma monoclonical anti-(AE1/AE3) and negatively stained for anti-cytolceratine (CAM5), high-molecular-weight keratine (HMWK), vimentin CD34, desmin, S-100, and HMB-45. These results strongly suggest that the lesion showing a sarcomatous appearance represents a sarcomatous change of the HCC rather than a complication of the HCC and sarcoma as result of repeated TAE. It is noteworthy that repeated TAE may be related to the development of sarcomatous HCC. Therefore, attention must be given to the occurrence of a sarcomatous lesion when TAE is performed in the case of HCC.

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INTRODUCTION

The basic histological pattern of an hepatocellular carcinoma (HCC) is a trabecular pattern that resembles the normal structure of the liver. However, it is also known that HCC exhibits various histological features even in the same cancerous nodule. Among these various histological features, the coexistence of a sarcomatous appearance has sporadically been reported (1-9). In many such cases, it is difficult to decide whether the HCC with a sarcomatous lesion is caused by sarcomatous changes in the HCC or by

complications involving the HCC and the sarcoma. The nature of the sarcomatous appearance in the HCC is not clearly understood (10).

Recent advances in medical treatments for HCC, such as transcatheter arterial embolization (TAE), percutaneous ethanol injection (PEI), percutaneous microwave coagulation, and radiofrequency ablation (RFA), have improved the local control and survival rates. While HCC cases with sarcomatous features are uncommon, the number of HCC cases with sarcomatous changes have risen markedly in recent years (11), and it is possible that the development of sarcomatous changes is connected to anticancer therapy. To our knowledge, there have been few reports of HCC with sarcomatous changes after TAE. We report herein a case of HCC with rapidly developing sarcomatous changes after TAE.

CASE REPORT

The patient was a 56-year-old man with a 20-year history of chronic liver disease related to alcoholic hepatitis. He consumed approximately 500 ml ~ 600 ml of alcohol daily. His liver function was mildly injured, and the serum hepatitis B virus (HBV) and hepatitis C virus (HCV) were not detected. Furthermore, he had no history of autoimmunohepatitis. Accordingly, these results demonstrated that his liver dysfunction was due to alcoholic injury. At the same time, he was receiving medication for antihypertension and diabetes mellitus. In November 2004, small, multiple space-occupying lesions (SOLs) were detected during an abdominal ultrasonography. As a result, the patient was admitted to the hospital in February 2005 for the treatment of an HCC tumor measuring 2 cm in diameter in segment II, another measuring 1 cm along with two smaller HCC tumors in segment VI, and a small 6 mm HCC tumor in segment VII of the liver. The first TAE was performed on the lesion of the HCC tumor in segment II (Fig. 1) because hypervascularity was demonstrated during angiography in that segment of the liver. After the TAE procedure, the follow-up was conducted at the Nagami Clinic. The patient's liver function was almost normal, and the status of diabetes mellitus was also within normal limits. In June 2005, a second TAE was performed to the HCC tumor in segments

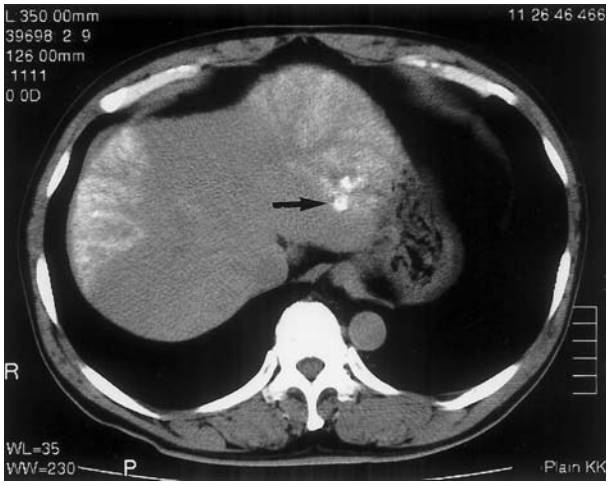

Fig. 1. A dynamic arterial phase CT in February 2005 demonstrates a hypervascular tumor in segment II (→) of the liver and another tumor in segment VI.

V and VI. At this point, an abdominal dynamic arterial phase computed tomography (CT) demonstrated that the HCC tumors in segments V and VI were strongly stained, and TAE was performed on these segments. Lipiodol CT demonstrated that there were no new HCC tumors in segment II and that the two HCC tumors in segments V and VI were filled with sufficient lipiodol (Figs. 2 and 3). In December 2006, a lipiodol CT was performed and demonstrated the recurrence of an HCC in segment VI; therefore, a third TAE targeted that recurrence (Figs. 4 and 5). In April 2007, the patient was admitted to the Matsue Red Cross Hospital with high fever, general fatigue, abdominal distension, and leucocytosis. Laboratory testing upon admission yielded the following findings: serum albumin, 3.0 g/dl; serum bilirubin, 1.2 mg/dl; aspartate aminotransferase (AST), 50 IU/l; alkaline aminotransferase (ALT), 46 IU/l; lactate dehydrogenase (LDH), 269 IU/l; alkine phosphatase (ALP), 408 IU/l; gamma glutamyltranspeptidase, 144 IU/l; indocyanine green 15-min retention, 22%; serum C-reactive protein (CRP), 0.48 mg/dl (standard level; <0.2 mg/dl); serum alpha-fetoprotein (AFP), 8 ng/ml (<10 ng/ml); protein induced by vitamin K absence or antagonist-II (PIVKA-II), 37 mAU/ml (<40 mAU/ml); serum carcinoembryonic antigen (CEA), 3.5 ng/ml (<5.0 ng/ml); CA19-9, 28 U/ml (<40 U/ml). A dynamic CT upon admission demonstrated that an HCC with an 8cm-diameter tumor in segment VI extrahepatically invaded adjoining organs (Figs. 6 and 7). A percutaneous tumor biopsy showed that the

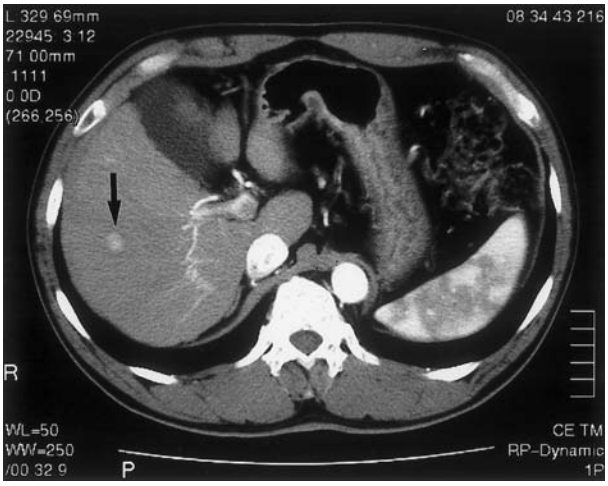

Fig. 2. A lipiodol CT demonstrated that the HCC tumor in segment V was filled with enough lipiodol (→).

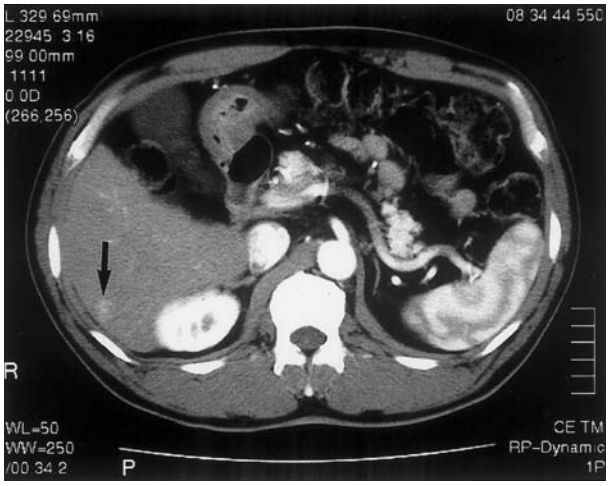

Fig. 3. A lipiodol CT demonstrated that the HCC tumor in segment VI was filled with enough lipiodol (→).

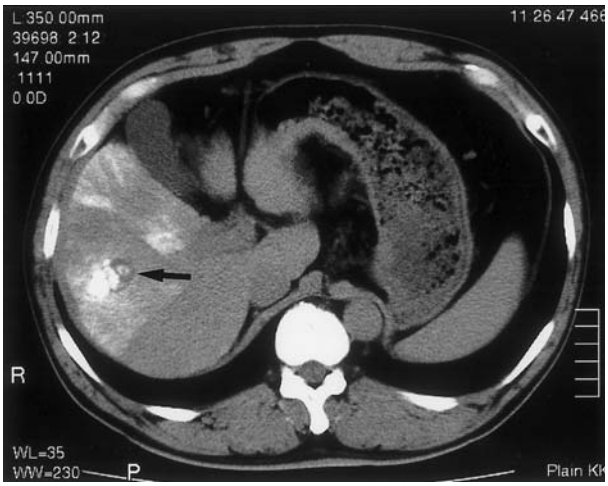

Fig. 4. In December 2006, a lipiodol CT was performed and demonstrated the HCC recurrence in segment VI (→).

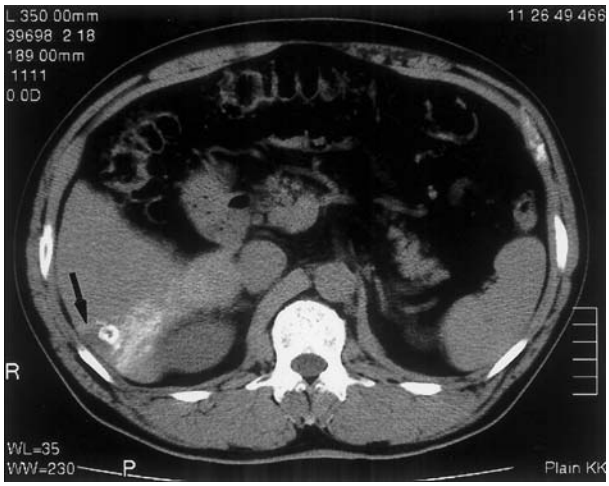

Fig. 5. In December 2006, a lipiodol CT was performed and demonstrated the HCC recurrence in segment VI (→).

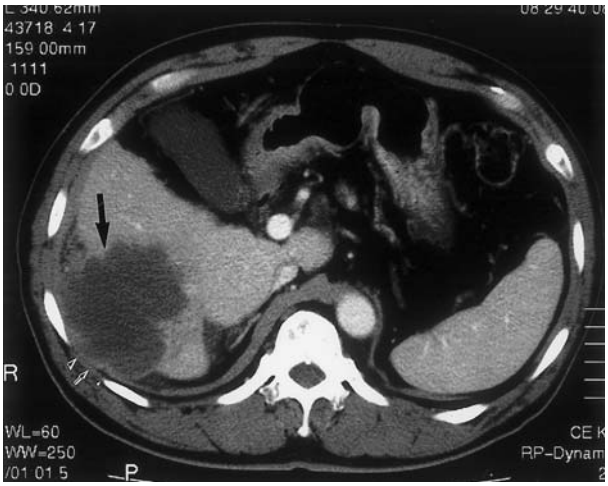

Fig. 6. In April 2007, a dynamic CT upon admission demonstrated that an HCC with an 8cm-diameter tumor in segment VI extrahepatically invaded adjoining organs (→).

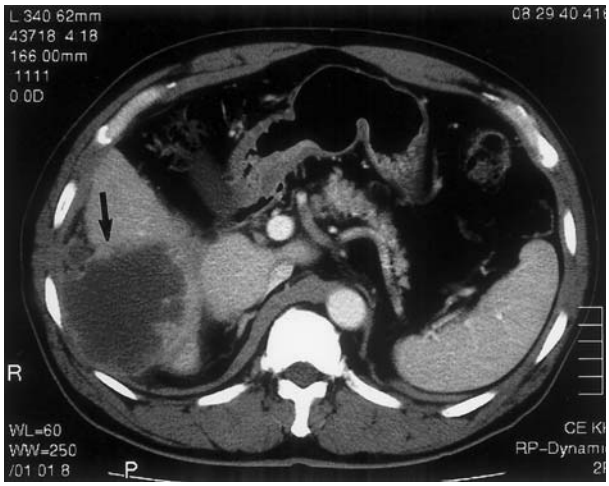

Fig. 7. In April 2007, a dynamic CT upon admission demonstrated that an HCC with an 8cm-diameter tumor in segment VI extrahepatically invaded adjoining organs (→).

main tumor was mainly composed of necrotic tumor tissues, fibrosis, and extremely little tumor-like tissue free from necrosis. The tissue free of necrosis was edematous and contained spindle-oval-shaped atypical cells with hyperchromatic nuclei and giant atypical cells with swollen nucleolar bodies, which is a sarcomatous feature. The tumor stain of the HCC in segment VI disappeared after the fourth therapy of TAE in segment VI of the liver. In May 2007, a local recurrent tumor of 1.5 cm in segment VI and a new nodule of 1 cm in diameter were detected in segment VI. Bone metastasis developed, and the main tumor in segment VI grew rapidly. A dynamic CT revealed that the hypervascular tumor in segment VI had rapidly enlarged to 14 cm in diameter and progressed to extrahepatic proliferation in May 2007.

Target needle biopsy of the tumor in segment VI revealed diffuse involvement of spindle-shaped sarcomatoid cells. An immunohistochemical study showed that the sarcomatoid cells were positively stained for SMA, c-KIT, vimentin, S-100, and epithelial membrane antigen (EMA). The patient's general condition deteriorated rapidly, and he died on July 1, 2007.

Autopsy findings showed a massive hepatic necrotic hemorrhagic tumor measuring 14 cm and involving segment VI with massive invasion into the diaphragm (Figs. 8 and 9). Several nodules were scattered through segments IV, V, and VIII. Lymph node metastases were observed in the paragastric, retroperitoneal, and lung hilar regions. Histologically, the massive hepatic tumor consisted of spindle cells or pleomorphic cells (Fig. 10). Other nodules were diffusely involved in the necrosis and partially remained as well to moderately differentiated trabecular HCC (Fig. 11). There was no transitional line between the HCC and sarcomatous spindle cells. An immunohistochemical study showed that the sarcomatoid cells were positively stained for SMA, c-KIT,

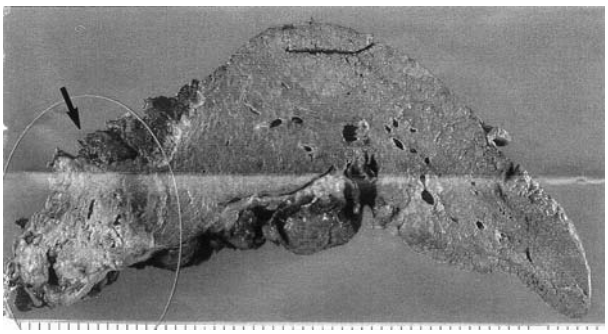

Fig. 8. Autopsy findings showed a massive hepatic necrotic hemorrhage measuring 14 cm in the tumor (→).

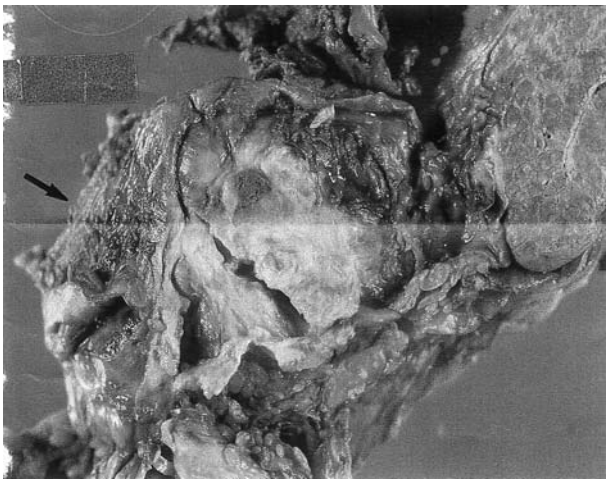

Fig. 9. Autopsy findings showed a massive hepatic necrotic hemorrhage measuring 14 cm in the tumor (→).

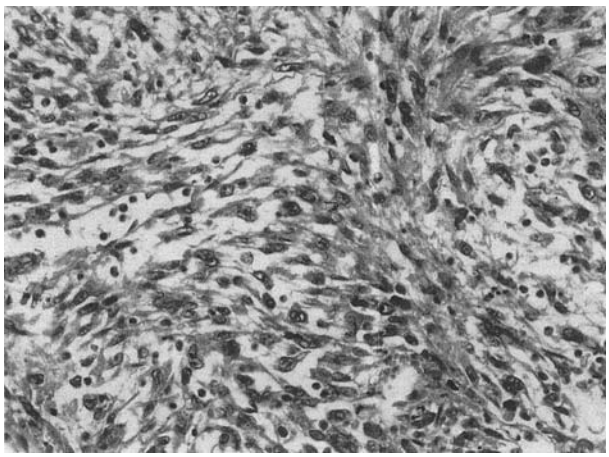

Fig. 10. A histological examination during autopsy showed a massive hepatic tumor consisting of spindle cells or pleomorphic cells.

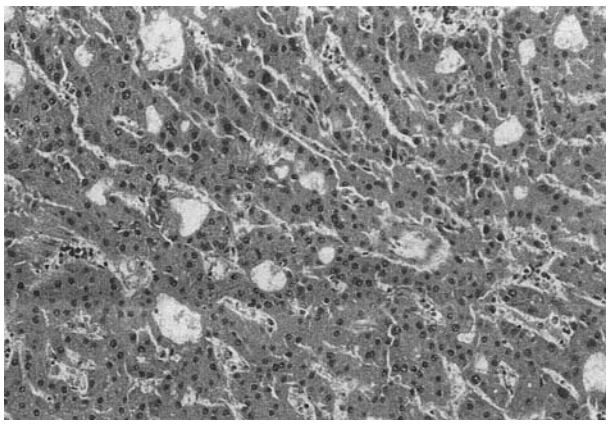

Fig. 11. A histological examination during autopsy showed a hepatic tumor consisting of well to moderately differentiated trabecular HCC.

and AE1/AE3 and negatively stained for CAM5, HMWK, vimentin CD34, desmin, S-100, and HMB-45.

These results confirmed that the tumor was compatible with a sarcomatous hepatic cellular carcinoma.

DISCUSSION

Edomonson and Steiner (2) reported that an HCC with a sarcomatous appearance was a carcinosarcoma, and they speculated that it could represent two independent tumors in collision; a second less likely possibility was that the spindle cells represented a peculiar metaplasia of liver cell carcinoma. Leevy *et al.* (12) defined the carcinosarcoma and sarcomatous elements. Isomura (6) reported a case in which a part of an HCC showed a transition from a trabecular HCC to a sarcomatous appearance, and he regarded it as a sarcomatous change. Tsujimoto *et al.* (9) reported a similar case as a sarcomatous change. On the other hand, Jaffe (1), Shin *et al.* (7), and Nagamine *et al.* (8) interpreted an HCC with a sarcomatous appearance to be a double cancer, i.e., an HCC and a hepatic sarcoma. Kuwano *et al.* (4) reported a case of an HCC with osteoblast-like giant cells and considered it to be an association of an HCC and a sarcoma; however, they did not rule out the possibility that it might be a product of the metaplasia of an HCC.

The present case developed a sarcomatous carcinoma during treatment for a well-differentiated HCC. The differential diagnosis of a sarcomatous carcinoma from true sarcomas is not always easy. Most sarcomatous areas associated with hepatic tumors are considered to be sarcomatous carcinomas, not true sarcomas. In the present case, the autopsy showed tumors with sarcomatous features and an ordinary HCC. Furthermore, an immunohistochemical study demonstrated positive staining for SMA, c-KIT, and AE1/AE3, while CAM5, HMWK, vimentin, CD34, desmin, S-100, and HMB 45 stains were negative in the sarcomatous areas. In general, SMA is stained specifically in epithelial cells, and vimentin is stained in mesenchymal cells (13). Because our case had both the epithelial and mesenchymal phenotypes in the sarcomatous area, it was diagnosed to be a sarcomatoid carcinoma originating from an HCC.

The incidence of HCC with sarcomatous change is reported to be 2.2-9.4% in primary liver cancers (13,14). This incidence has increased remarkably over the past several years (11). One of the causes is indicated to be anticancer therapy. In fact, a sarcomatous appearance was found in 20.9% of HCC that had undergone anticancer therapy (11), such as a one-shot injection of anticancer agents into the hepatic artery or TAE. In contrast, a sarcomatous appearance was seen in only 4.2% of HCC that underwent conservative therapy (11).

The mechanism of sarcomatous changes by anticancer therapy remains unknown. It is only presumed that anticancer therapy induces a phenotypic change in HCC cells. Although the present case repeatedly received TAE, a tumor biopsy performed in May 2007 demonstrated that it was moderately differentiated HCC. In dynamic CT, local recurrent tumors after TAE were hypervascular. Furthermore, considering that the sarcomatous HCC progressed very rapidly from May 2007, it is quite unlikely that a sarcomatous HCC was present before TAE. Therefore, it is highly possible that TAE was the cause of the phenotypic conversion from moderately differentiated HCC to sarcomatous HCC. In fact, it has been reported that thermal stress increases oxidative DNA modifications (15) and induces chromosomal gains and/or losses *in vitro* (16). Therefore, thermal stress is a potential carcinogenic or mutagenic factor. HCC cells remaining viable after TAE may result in phenotypic conversion to a sarcomatous tumor. Seki *et al.* (17) have also reported an HCC that progressed rapidly after TAE. This report supports the possibility that TAE induces a morphological change in tumor cells. Further studies with sufficient cases as a long-term follow-up are needed to clarify this. The present case indicates that TAE may cause a sarcomatous change and that complete necrosis with a sufficient safety margin is indispensable in the treatment of HCC.

The basic growth pattern of HCC in the liver is the replacing pattern, whereas that of tumor cells with sarcomatous appearance shows a sinusoidal growth pattern. The sinusoidal growth pattern is commonly observed in poorly differentiated HCC, and extrahepatic metastasis has been reported to be more frequent in HCC with a sinusoidal growth pattern

(18,19). This may be a reason for the high incidence of extrahepatic metastasis in cases with a sarcomatous appearance. An additional characteristic finding is the presence of advanced necrosis in the tumor.

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