

Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy

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Summary. Among 579 autopsy cases of hepatocellular carcinoma (HCC), 55 cases (9.4%) exhibited a sarcomatous appearance. The incidence of HCC with a sarcomatous appearance has been increasing over the past 17 years. A sarcomatous appearance was found in 20 out of 335 autopsy cases of HCC (5.9%) during the 12 years from 1969 to 1980, and in 35 out of 244 autopsy cases of HCC (14.3%) during the last 6 years, when effective anticancer therapies, such as the one-shot injection of anticancer agents into the hepatic artery (one-shot therapy) and transcatheter arterial embolization (TAE), have become popular. A sarcomatous appearance was found in 20.9% of the cases undergoing anticancer therapy and in 4.2% of the cases not undergoing anticancer therapy. Among the various anticancer therapies, the sarcomatous appearance was most frequent (27.6%) in cases with repeated TAE. Thus, a close relationship between the sarcomatous appearance in HCC and anticancer therapies was suggested. Regarding the development of the sarcomatous appearance, we presume that it may be caused by the phenotypic change of HCC cells caused by anticancer therapy, or that a number of factors, including anticancer therapy, may accelerate the proliferation of the sarcomatous cells existing in the original tumor as one of the histological components. In order to clarify the true nature of sarcomatous lesions in HCC, further histological and biological studies are required.

Introduction

It is well known that hepatocellular carcinoma (HCC) frequently exhibits various histological features in addition to the basic trabecular pattern. Among such histological varieties, the existence of a sarcomatous appearance has been reported sporadically [3, 5, 6, 11, 12, 16, 17]. Although it is considered that the sarcomatous appearance is caused by either a sarcomatous change of part of the HCC or the coexistence of sarcoma and HCC, our previous study, using an immunohistochemical technique on HCC with a sarcomatous appearance, suggested that it seemed to be caused by a sarcomatous change of part of the HCC in most of those cases [8].

We report here on the pathomorphological characteristics of HCC exhibiting a sarcomatous appearance with reference to the relationship with anticancer therapy.

Materials and methods

Fifty-five cases, which histologically exhibited a sarcomatous appearance, were chosen from 579 autopsy cases of HCC at the Pathology Department of Kurume University Hospital during the past 17 years from 1969 to 1986. The clinical data of the cases were obtained from the patients' charts.

The livers were fixed in 10% formalin and cut into 0.5–1.0-cm slices to facilitate careful gross examination. Each slice was divided into 20–30 blocks, which were then embedded in paraffin and stained with hematoxylin and eosin and reticulin.

The data were statistically analyzed by the χ^2 test.

Results

Frequency

A sarcomatous change was found in 55 cases out of 579 autopsy cases of HCC (9.4%). The incidence of HCC with a sarcomatous change has been increasing over the past 18 years (Fig. 1). A sarcomatous change was found in 20 cases out of 335 autopsy cases of HCC (5.9%) during the 12 years from 1969 to 1980, and in 35 cases out of 244 autopsy cases of HCC (14.3%) during the last 6 years from 1981 to 1986.

HCC with a sarcomatous appearance and anticancer therapy

Among the 244 autopsy cases of HCC during the 6 years from 1981 to 1986, the detailed records of the anticancer therapy applied were available for 170 cases. In these 170 cases, a sarcomatous appearance was found in 18 out of the 86 cases of HCC (20.9%) that had undergone anticancer therapy, and in 2 out of the 48 cases (4.2%) which had undergone only conservative therapy. Looking at the various anticancer therapies, a sarcomatous appearance was found in 8 of the 36 cases (22.2%) that had received a one-shot injection of anticancer agents into the hepatic artery (one-shot therapy) and in 16 of the 49 cases (20.4%) treated with transcatheter arterial embolization (TAE). A sarcomatous appearance was seen in 8 of the 29 cases (27.6%) which had received TAE more than twice. The incidence of HCC with a sarcomatous appearance is significantly higher in groups which had undergone anticancer therapy ($P < 0.05$).

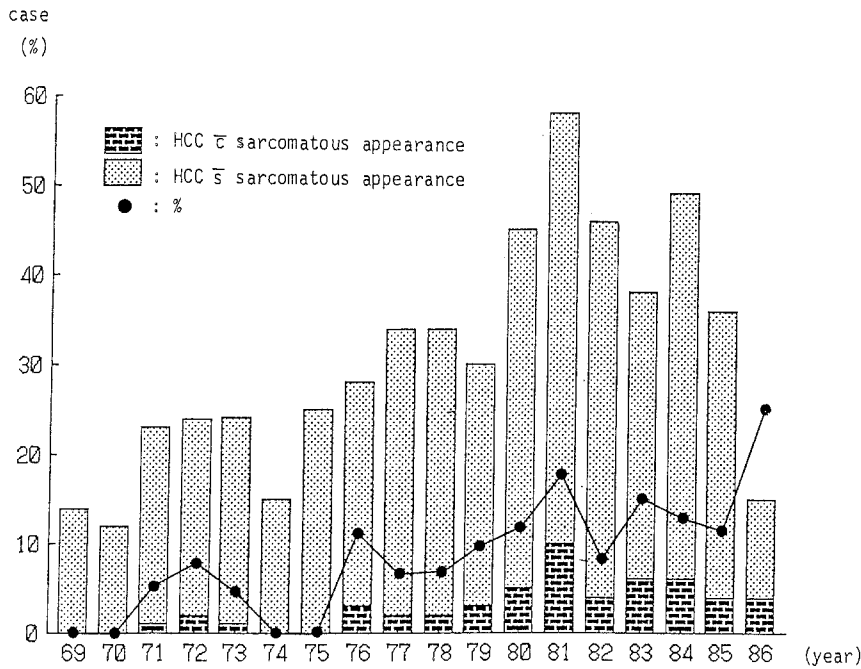


Fig. 1. The transition of the incidence of hepatocellular carcinoma with a sarcomatous appearance (year)

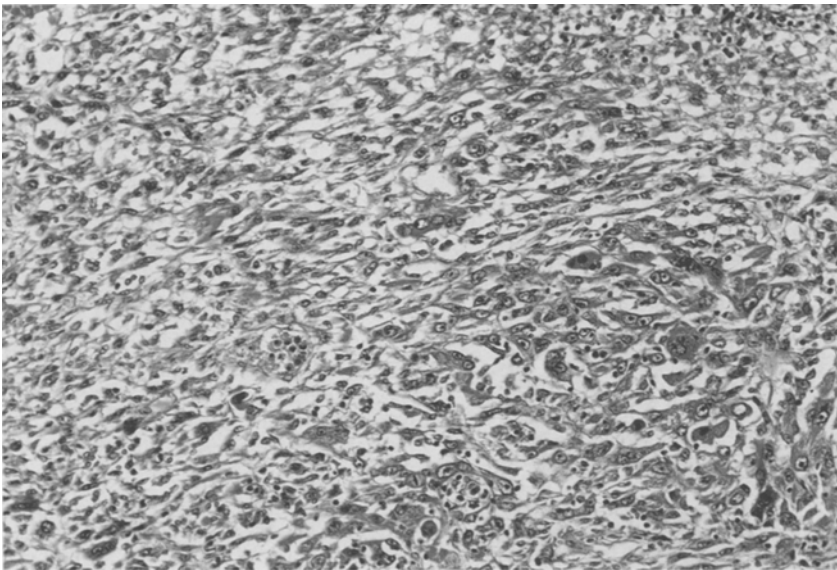


Fig. 2. Sarcomatous appearance, spindle-cell type. A sarcomatous tumor consists mainly of spindle-shaped cells showing occasional pleomorphism (hematoxylin/eosin, $\times 100$)

Survival time

The survival time from the appearance of an initial sign ranged from 1 month to 32 months with a mean of 6.2 ± 3.3 months among the cases with a sarcomatous change. The mean survival times for the patients who had undergone only conservative therapy was 6.7 ± 2.2 months. There was no significant difference between the two groups.

α -Fetoprotein

Among the 42 cases in which the serum α -fetoprotein levels were examined, these levels were 20 ng/ml or less in the 17 cases with a sarcomatous appearance (40.4%). α -Fetoprotein was negative in 13 of the 182 cases without a sarcomatous appearance (7.1%). The number of α -fetoprotein-negative cases was significantly greater than that of the control ($P < 0.05$).

Pathological characteristics

Gross findings. According to our gross classification [13], 26 cases were classified as the infiltrative type, 25 cases were classified as the mixed expansive and infiltrative type, and 4 cases were classified as the pedunculated type.

Histological findings. The sarcomatous appearance could be categorized into two types: that consisting mainly of spindle-shaped cells (spindle-cell type) (Fig. 2), and that consisting of tumor cells which lacked mutual contact (free-cell type) (Fig. 3). Both types were accompanied by varying degrees of pleomorphism.

The lesion showing a sarcomatous appearance of the spindle-cell type looked like fibrosarcoma or leiomyosarcoma. Among the 55 cases with a sarcomatous appearance, 14 cases were of the spindle-cell type, 35 cases were

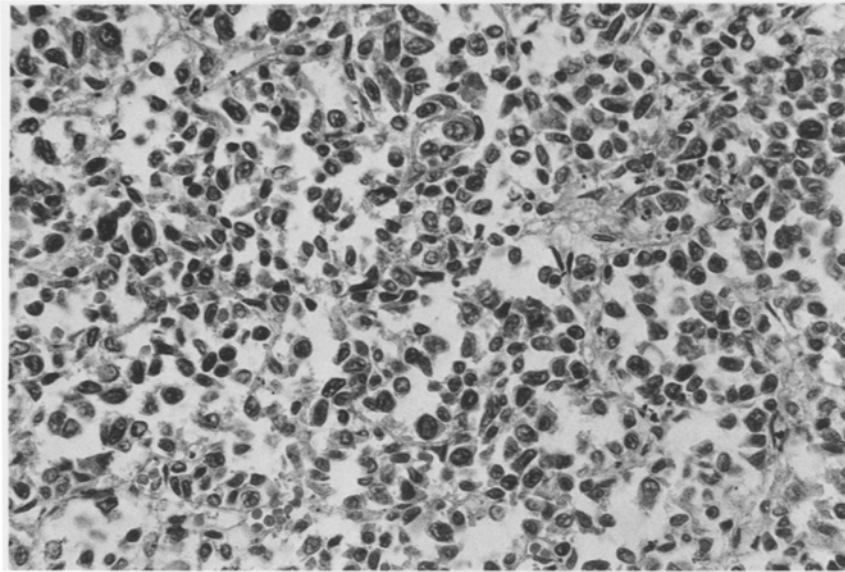


Fig. 3. Sarcomatous appearance, free-cell type. Most of the tumor cells are round and lack mutual contact (hematoxylin/eosin, $\times 200$)

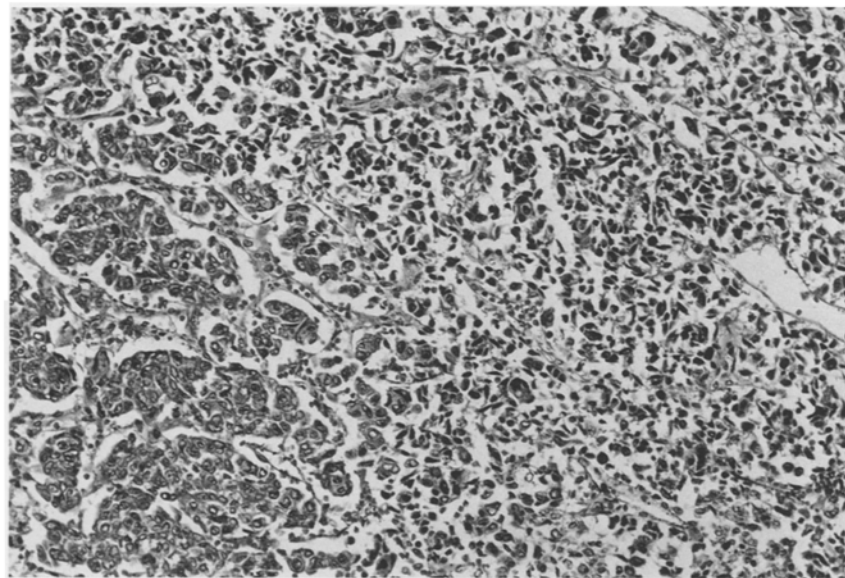


Fig. 4. The characteristic of transition from the trabecular pattern of hepatocellular carcinoma to the sarcomatous appearance of the free-cell type (hematoxylin/eosin $\times 100$)

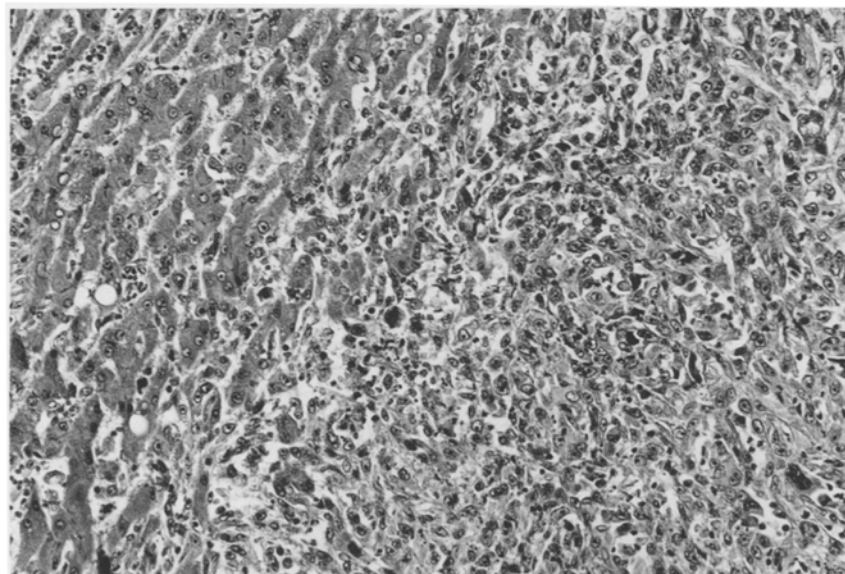


Fig. 5. The tumor cells are proliferating in a sinusoidal growth pattern (hematoxylin/eosin, $\times 100$)

of the free-cell type, and 6 cases were a mixture of both types. In two cases, the tumors had only the sarcomatous appearance of the spindle-cell type. The characteristic suggesting a transition from a trabecular pattern of HCC to a sarcomatous appearance was found in 4 of the 14 cases of the spindle-cell type and in most of the 35 cases of the free-cell type (Fig. 4). All tumors exhibiting a sarcomatous appearance showed a sinusoidal growth pattern [14], in which the tumor cells had grown infiltratively along the sinusoid, at the tumor/non-tumor boundary (Fig. 5).

Metastasis

Extrahepatic metastasis was observed in 42 of the 55 cases (76.3%). Metastasis was thought to be hematogenous in 38 cases (69%), lymphatic in 32 cases (58.1%), and disseminated in 15 cases (23.3%). In the cases without a sarcomatous appearance, hematogenous metastasis was seen in 48.9%, lymphatic metastasis was seen in 29.4%, while disseminated metastasis was seen in 23.3%. The frequency of extrahepatic metastasis, particularly lymphatic metastasis, was significantly higher in HCCs with a sarcomatous appearance ($P < 0.01$).

Discussion

It is known that epithelial malignant tumors, including lung cancer, mammary cancer and esophageal cancer, often exhibit a sarcomatous appearance, and they are called carcinosarcoma [1, 2, 10, 15].

In HCC, Edmondson and Steiner [4] encountered two cases which were hard to distinguish from sarcoma and one case with a partly sarcomatous appearance among 100 autopsy cases of HCC. Isomura et al. [5] and Tsujimoto et al. [17] each reported a case in which a part of a HCC showed a transition from a trabecular HCC to a sarcomatous appearance, and considered that the sarcomatous appearance was a transformation of the HCC. Meanwhile, some reports have interpreted HCC with a sarcomatous appearance as the double cancer of HCC and hepatic sarcoma [3, 6, 11].

As for the histogenesis of sarcomatous cells in HCC, our previous study on HCC with a sarcomatous appearance, using an immunohistochemical technique, revealed that most of the tumor cells in the regions of sarcomatous appearance were frequently found to be positive to keratin, albumin and fibrinogen, and these results strongly suggested that the lesions showing a sarcomatous appearance represented the sarcomatous change of HCC rather than the association of HCC and sarcoma [8].

Histologically, a sarcomatous lesion seen in HCC could be divided into two types: the spindle-cell type and the free-cell type. The tumor cells of both types show an infiltrative growth in the liver, and the frequency of metastasis was significantly higher than that of HCC of the common type. In particular, lymphatic metastasis was almost twice as frequent as that of HCC without a sarcomatous appearance. Tsujimoto et al. [17] also reported widespread metastasis in a case of HCC with a sarcomatous appearance. Kawabata [9] reported that massive lymph node metastasis was more frequent in HCC with a sarcomatous appearance than in HCC of the trabecular type according to a study of 19 cases of HCC with massive lymph node metastasis.

The existence of a certain correlation between α -fetoprotein and tumor histology has been noted. According to an analysis made by the Liver Cancer Study Group of Japan, moderately differentiated HCC, corresponding to Edmondson-Steiner's grades II to III, were frequently positive for α -fetoprotein, but well or poorly differentiated HCC, corresponding to grade I or IV, tended to be negative [7]. Among the 55 cases with a sarcomatous appearance, about 40% of the cases were negative for α -fetoprotein, while the positive rate for α -fetoprotein was significantly lower compared to that of HCC of the common type.

It is interesting evidence that the incidence of HCC with a sarcomatous appearance has increased remarkably over the past several years when effective anticancer therapies, such as one-shot injection and TAE, have become popular. Furthermore, the incidence of HCC with a sarcomatous appearance is significantly higher in cases undergoing anticancer therapy. Thus, a close relationship between the sarcomatous appearance in HCC and anticancer therapy has been suggested.

Regarding the development of the sarcomatous appearance in HCC, we presume that it may be caused by the phenotypic change of HCC cells caused by anticancer therapy, or that a number of factors including anticancer therapy may accelerate the proliferation of sarcomatous cells, which existed in the original tumors as one of the histological components. In order to clarify the true nature of sarcomatous lesions seen in HCC, however, further histological and biological studies are required.

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