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ORIGINAL ARTICLE

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원발성 간혈관육종의 임상적 고찰: 8예 분석

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Clinical Courses of Primary Hepatic Angiosarcoma: Retrospective Analysis of Eight Cases

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Background/Aims: Hepatic angiosarcoma, a rare and aggressive liver malignancy, is difficult to diagnose because of a lack of specific clinical features. The clinical and radiological features of patients with histologically confirmed hepatic angiosarcoma were examined.
Methods: Among 2,336 patients diagnosed with primary hepatic carcinoma at Keimyung University Dongsan Medical Center (Daegu, Korea) between May 2002 and February 2012, eight (0.03%) with histologically confirmed primary hepatic angiosarcoma were included. The patterns of disease diagnosis, tumor characteristics, treatment responses, and prognoses were reviewed retrospectively.
Results: Median age was 66 years-old (range, 41-80 years). Four patients were male. Five patients were compulsive drinkers. All patients had no HBsAg and anti-HCV. Initial radiologic diagnoses revealed primary hepatic angiosarcoma (n=2), hepatocellular carcinoma (n=2), hemangioma (n=2), and hepatic metastatic carcinoma (n=2). Definitive diagnoses were made by percutaneous needle biopsies in seven patients and surgical resection in one patient. At the time of the initial diagnosis, extrahepatic metastases were detected in three patients (37.5%). Metastatic sites included the spleen and lung, pericardium, and bone, in one patient each. Two patients underwent conservative treatments. The remaining patients underwent surgical resection (n=1), transcatheter arterial chemoembolization (n=1), and systemic chemotherapy (n=4). The median survival period was 214 days (range, 21-431 days).
Conclusions: Hepatic angiosarcoma is a highly progressive disease with a poor prognosis. Detailed studies including histological examinations are essential to facilitate early diagnosis of the disease. **(Korean J Gastroenterol 2015;65:229-235)**

Key Words: Hepatic angiosarcoma; Liver neoplasms

INTRODUCTION

Hepatic angiosarcoma is a very rare mesenchymal malignancy accounting for < 2% of all primary liver tumors.[1] Its epidemiological data are limited and, in most cases, etiology is not clearly defined.[2] Some studies have suggested that hepatic angiosarcomas were associated with chronic exposure to thorotrast, vinyl chloride, arsenic, radium, and anabolic steroids, and were possibly related to alcoholic cirrhosis and chronic idiopathic hemochromatosis.[3,4]

Early diagnosis of hepatic angiosarcoma is difficult owing to its non-specific symptoms, including abdominal pain,

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weakness, and weight loss.[3] In addition, the radiological features of hepatic angiosarcoma are not easily differentiated from those of hemangioma or other liver malignancies.

Characterized by a rapid progression, high recurrence rate, and resistance to traditional chemotherapy and radiotherapy, the patient survival rate for hepatic angiosarcoma is very low.[5-7] Since only a small portion of tumors are resectable at the initial diagnosis, curative liver resection is limited. In previous studies few patients exhibited long-term survival after hepatectomy.[8-12]

Therefore, we retrospectively reviewed the clinical features, radiologic findings, and treatment outcomes of eight patients with histologically confirmed primary hepatic angiosarcoma, in order to attain a better understanding of the disease by providing additional clinical data.

SUBJECTS AND METHODS

1. Patients

Among 2,336 patients with primary hepatic carcinoma, admitted to our institution between May 2002 and February 2012, eight patients with histologically confirmed primary hepatic angiosarcoma were enrolled. Clinical characteristics, patterns of disease diagnosis, radiological findings, sites of metastases, treatment responses, and survival outcomes were evaluated retrospectively.

2. Diagnosis

Radiological diagnoses were based on a review of the radiologic findings and confirmed by a senior radiologist. The radiological pattern was classified according to 4 types based on the classification by Ludwig and Hoffman,[13] including (1) multiple nodules; (2) a large dominant mass; (3) a mixed pattern of a dominant mass with nodules; and (4) diffusely infiltrating micronodular tumors. Definitive diagnoses were based on a review of the histological findings and were confirmed by a senior pathologist. Tumor samples were obtained by percutaneous needle biopsy or surgical resection. Immunohistochemical staining for CD31, CD34, and factor VIII-related antigen was performed to determine tumor origin; samples were confirmed as vascular tumors originating from endothelial cells when at least one of these factors was present.

3. Statistical analyses

Statistical analyses were performed using SPSS software for Windows (version 12.0; SPSS Inc., Chicago, IL, USA). Frequency variables were represented as frequencies with percentages. Overall survival rates were estimated using the Kaplan-Meier method. The following treatment variables (aggressive versus conservative) were compared using a log-rank test. A p-value of <0.05 was considered statistically significant.

4. Ethics statement

This study was approved by the instituitional review board of Keimyung University Dongsan Hospital (IRB No. 12-219). Informed consent was waived by the board.

RESULTS

1. Characteristics of patients with primary hepatic angiosarcoma

Patient characteristics are shown in Table 1. Median age was 66 years-old (range, 41-80 years). Four patients were male. Five patients were compulsive drinkers and three of them had liver cirrhosis. None of the patients had HBsAg or anti-HCV.

2. Radiologic findings of primary hepatic angiosarcoma

Five patients had multiple hepatic lesions with bilobular distribution. Among the four classifying growth patterns,[13-15] five patients had a mixed dominant mass with nodules, two had multiple nodules, and one had a large solitary mass (Table 1). Non-enhanced CT showed hypoattenuated lesions with or without hyperattenuated foci in six patients. Contrast-enhanced CT showed hypoattenuated lesions with centrally enhanced foci in six patients (Fig. 1). One patient showed an isoattenuated lesion with centrally enhanced foci and one patient showed a hypoattenuated lesion with peripheral ring enhancement (Fig. 2). Compared with the aorta, focally enhanced areas showed less attenuation and were irregularly shaped with central or peripheral ring enhancement. A delayed progressive enhancement pattern was observed in all enhanced lesions, except in one patient whose lesion was hypoattenuated with a peripheral ring enhancement. A typical enhancement pattern was found in five patients (Table 1).

Table 1. Characteristics of Patients and Clinical Findings with Primary Hepatic Angiosarcoma

Patient	Sex/ age (yr)	Chief complaint	Comorbidity	Growth pattern	Typical nature	Maximal diameter (mm)/ tumor (n)	Metastasis	TNM stage	Initial radiologic diagnosis	Immunohistochemical stain positive	Treatment	Survival time (day)
1	F/61	Bone pain	HTN	Multiple nodules	Atypical	70/8	Bone	$T_2N_1M_1$	Hepatic metastatic carcinoma	CD31, factor VIIIRA	Chemotherapy	431
2	M/64	Hemoptysis	Alcoholic LC	Mixed dominant mass withnodules	Atypical	132/1	Spleen, lung	$T_2N_1M_1$	Hepatocellular carcinoma	CD31, factor VIIIRA	Chemotherapy	427
3	F/41	Dyspnea	None	Multiple nodules	Typical	44/6	Pericardium, lung	$T_1N_1M_1$	Hemangioma	CD31, factor VIIIRA	Chemotherapy	375
4	M/62	Abdominal pain	Alcoholic LC	Mixed dominant mass withnodules	Atypical	80/6	None	$T_2N_0M_0$	Angiosarcoma	CD31	Chemotherapy	305
5	F/72	Abdominal pain	HTN	Mixed dominant mass withnodules	Typical	76/2	None	$T_2N_1M_0$	Hemangioma	CD31, factor VIIIRA	Transcatheter arterial chemoembolization	123
6	M/68	Abdominal pain	None	Large solitary mass	Typical	120/1	None	$T_2N_0M_0$	Angiosarcoma	CD31, CD34, factor VIIIRA	Operation	74
7	F/72	Abdominal pain	DM, HTN, CVA	Mixed dominant mass withnodules	Typical	140/1	None	$T_2N_1M_0$	Hepatocellular carcinoma	CD31, CD34, factor VIIIRA	Conservative	36
8	M/80	Abdominal pain	Alcoholic LC, AMI	Mixed dominant mass withnodules	Typical	128/3	None	$T_2N_0M_0$	Hepatic metastatic carcinoma	CD31, CD34	Conservative	21

HTN, hypertension; LC, liver cirrhosis; DM, diabetes mellitus; CVA, cerebrovascular attack; AMI, acute myocardial infarction; factor VIII RA, factor VIII related antigen.

Fig. 1. CT findings of a typical hepatic angiosarcoma. A huge hypervascular enhancing mass with a central necrotic portion can be seen in the right hepatic lobe. Most nodular lesions are hypoattenuated and have enhanced foci. The enhancement is less than that of aorta, and some nodular lesions show irregular or ring enhancement. A progressive enhancement pattern can be seen in the delayed phase CT.

Fig. 2. CT findings of an atypical hepatic angiosarcoma. Multiple peripheral enhancing nodules with a hypoattenuated center are scattered in the liver.

The initial CT-based diagnoses were hepatocellular carcinoma (n=2), hemangioma (n=2), and hepatic metastatic carcinoma (n=2), and primary hepatic angiosarcoma (n=2).

3. Immunohistochemical diagnostic features of primary hepatic angiosarcoma

A definitive diagnosis was based on a percutaneous needle biopsy in seven patients and surgical resection in one. The gross morphology of cut section showed reticular and cystic structure with formation of many large blood vessels. The vessels were irregular and mixed with grayish white solid structure. Tumor cells grew along the existing sinusoids, cen-

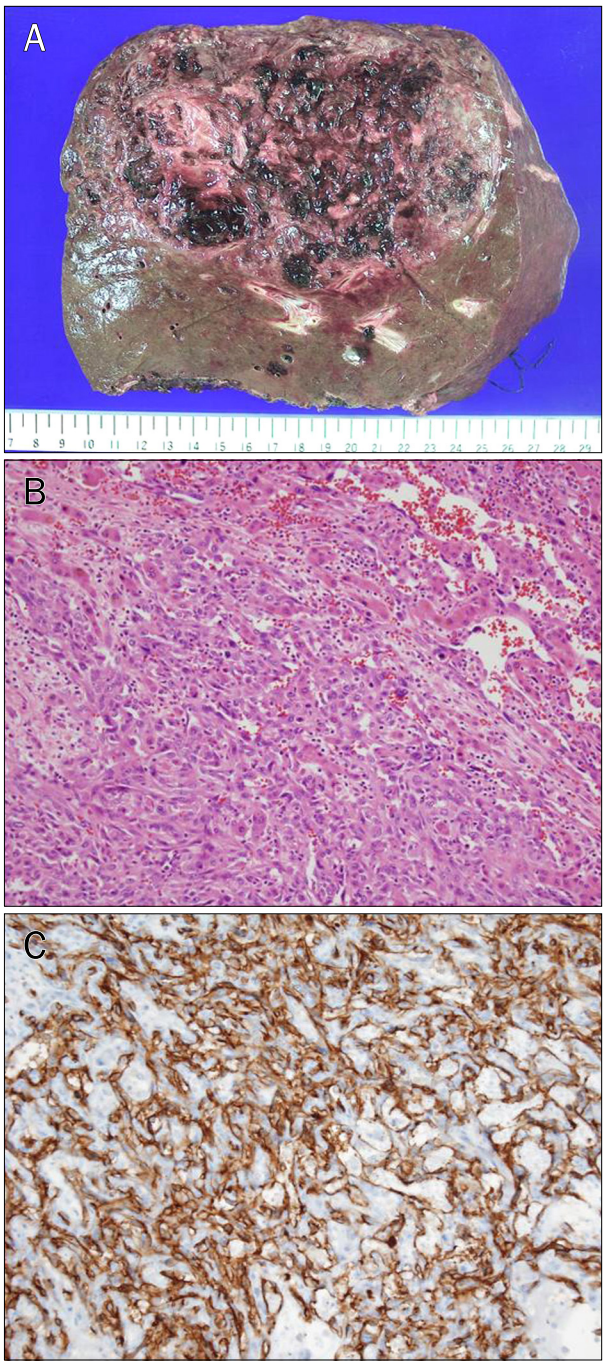

Fig. 3. Cut surface and microscopic findings of the liver. (A) Surgically resected right lobe, measuring up to 14.0×11.5×5.5 cm, showed an ill-defined large heterogeneous hepatic mass with solid, cystic nature. Diffusely scattered areas of hemorrhage and necrosis were seen in the mass. (B) Needle biopsy of the hepatic mass showed diffuse growth of pleomorphic hyperchromatic tumor cells with anastomosing vascular channels (H&E, ×200). (C) Immunohistochemical staining for CD31 showed diffuse, strong, positive reactivity in the atypical tumor cells (×200), demonstrating a vascular-type tumor originating from endothelial cells.

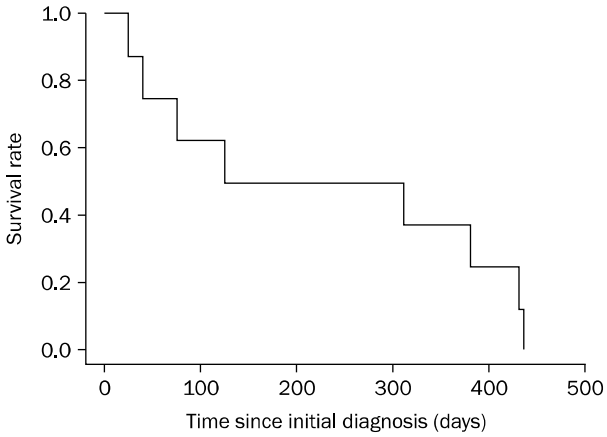

Fig. 4. Survival time of the hepatic angiosarcoma patients. The median survival period was 214 days (range, 21-431 days).

tral veins, and portal vein branches, leading to vessel obstruction and dilatation and the formation of purpura, as well as solid hemorrhage and necrosis (Fig. 3A).

Microscopic morphology showed diffuse growth of pleomorphic and hyperchromatic tumor cells with anastomosing vascular channels, lined by atypical endothelial cells (Fig. 3B).

Liver tissues of all patients stained positive for at least one of CD31, CD34, or factor VIII-related antigens. Two patients were positive for CD31, CD34, and factor VIII-related antigen, three were positive for CD31 and factor VIII-related antigen; one was positive for CD31 and CD34; one was positive for CD34 and factor VIII-related-antigen; and one was positive only for CD31 (Table 1 and Fig. 3C).

4. Treatment and prognosis of patients with primary hepatic angiosarcoma

A number of patients presented with advanced stage at the initial diagnosis. Extrahepatic metastases were detected in three patients (37.5%), with sites including the spleen and lung, pericardium and lung, and bone in one patient each. Treatment regimens are shown in Table 1. The two patients who underwent conservative treatments had poor performance scores (Eastern Cooperative Oncology Group grade 3) and decided against aggressive therapies. Other treatments included surgical resection (n=1), transcatheter arterial chemoembolization (TACE, n=1), and systemic chemotherapy (n=4). Three patients administered doxorubicin/ifosfamide as the first-line chemotherapy showed progressive disease and were subsequently treated with docetaxel or paclitaxel. The cause of death was cancer progression in seven patients

and sepsis in one patient. The median survival period was 214 days (range, 21-431 days) (Fig. 4).

DISCUSSION

Angiosarcomas, which are soft-tissue tumors originating from endothelial cells, are associated with poor prognosis.[1] Primary hepatic angiosarcoma account for 4% of all angiosarcomas[16] and 1.8% of all hepatic malignancies.[17] Primary hepatic angiosarcoma mainly occurs in the elderly (60-70 years old), with a male to female ratio of 4 : 1.

Due to their shared similar hypervascular characteristics, radiological differentiation of hepatic angiosarcoma from malignancies such as hepatoma, hemangioma, metastatic liver malignancy, or adenoma is complicated. The difficulty of diagnosing hepatic angiosarcoma based on radiological findings alone was highlighted in the current study. Typical radiological patterns of hepatic angiosarcoma have been previously characterized as hypoattenuated lesions with or without hyperattenuated foci in non-enhanced CT images, and hypoattenuated nodular lesions with enhanced foci, with enhancement less than that of the aorta and irregular or ring enhancement, in contrast-enhanced CT images. In addition, a progressive enhancement pattern has been described in delayed CT images. Heterogeneity in radiological patterns has been attributed to differences in the microscopic vascular pattern between lesions; enhancement progresses more rapidly if sufficient anastomosing vascular channels are present, and more slowly if dilated cavernous vascular spaces are present.[15,18] Five of the eight patients in the current study presented with typical radiological findings, although only two were initially diagnosed with hepatic angiosarcoma. In addition, other studies employing ultrasonography, CT, and MRI have indicated that hepatic angiosarcoma does not always exhibit typical patterns, as seen in three of the eight patients in the current study.[1,19,20]

Determining the morphological changes that occur as a multiple nodular liver lesion progresses toward a diffuse infiltrative micro-nodular liver lesion could be useful in aiding the diagnosis of hepatic angiosarcoma.[21] In addition, heterogeneous signal intensities and central septal-like progressive enhancement on MRI scans might be suggestive of hepatic angiosarcoma.[22]

Considering the probability of differential diagnoses based on radiological examination alone, a histological examination is recommended as the best approach to confirm primary hepatic angiosarcoma. However, the vascular nature of hepatic angiosarcoma implies a tendency toward hemorrhage, which can make percutaneous biopsy dangerous.[23] In this study, none of the patients who underwent a percutaneous needle biopsy showed any signs of hemorrhage or inflammation. Furthermore, based on the histological analyses here, the radiological data was only accurate in two of the eight patients. The two patients who were initially diagnosed with hepatic hemangioma radiologically, but whose clinical course was incongruent with hemangioma were confirmed as having hepatic angiosarcoma in the final diagnosis made by histological analysis of the liver biopsy. One of these patients presented with abdominal pain that was nonresponsive to analgesics, whereas the other showed malignant pericardial effusion of unknown origin. These results support the necessity of more detailed investigations when angiosarcoma is suspected such as in case of rapid tumor growth, tumor rupture, increasing pain, or an incongruent clinical course.[24]

Reticular or cystic-like tumor cells are associated with the formation of tumors with multiple large blood vessels. However, tumors that exhibit proliferation of small blood vessels with characteristic silt-like lumens may take the form of grayish-white solid structures.[13,14] In the liver, tumor cells grow along the existing sinusoids, central veins, and portal vein branches accompanied by liver tissue atrophy, causing vessel obstruction and dilatation and the formation of purpura, as well as solid hemorrhage and necrosis.[24,25] The channels are lined by atypical endothelial cells with enlarged hyperchromatic nuclei. Tumors of vascular origin such as cavernous hemangioma, epithelioid hemangioendothelioma, Kaposi's sarcoma, fibrosarcoma, and leiomyosarcomas require pathological examination for differentiation.[26]

Immunohistochemical staining can be used to confirm the histological findings. All patients in the current study had confirmed vascular tumors originating from endothelial cells, in that each stained positive for CD31, CD34, or factor VIII-related antigens.

In the current study metastases from hepatic angiosarcoma were noted in the spleen, lung, pericardium, and bone.[27] This is likely because diagnosis of angiosarcoma is often delayed because of its non-specific symptoms. In most cases,

patients present with advanced stage disease because of the rapid progression and growth of the tumor, further suggesting the need for more information on the course of angiosarcoma to prevent an erroneous differential diagnosis.

For treatment, if a lesion is local, surgical resection is recommended.[28] Zhou et al.[11] reported an increase in overall survival of > 10 months after complete surgical resection. In the current study, one patient with localized hepatic angiosarcoma without metastasis underwent successful surgical resection, but died due to cancer recurrence after 74 days, which was much less than the median overall survival time. Such poor prognosis, despite successful surgical resection, is likely related to the large size of this patient's tumor when diagnosed. Furthermore, in many cases, curative treatment is not possible at the time of diagnosis because of the delay in definitive diagnosis and advanced disease stage, and a liver transplant is considered the only available treatment option.

Hepatic angiosarcoma has a high recurrence rate and a low postoperative survival rate, as demonstrated in the current study, where the median and mean survival times were < 8 months. The longest survival time noted to date is ~28 months.[27-29] Park et al.[18] reported that patients with a tumor response after TACE survived for > 8 months. Locker et al.[3] reported that 2 out of 4 patients who had chemotherapy died within 3 months of diagnosis; the other 2 survived for > 6 months, but prognosis was very poor and the median survival time without aggressive treatment was < 6 months,[1,3] with only 3% of the patients having survived longer than 3 years.[3] Overall, prognosis for angiosarcoma is dismal, further supporting the need for standardized diagnostic protocols.

In conclusion, to improve the prognosis for patients with hepatic angiosarcoma, extensive analysis including a histological examination is crucial for early diagnosis to enable appropriate treatment, such as surgical resection, prior to rapid tumor expansion or development of metastases. In addition, development of more effective systemic, local, or molecular-targeted therapies is urgently required in order to improve clinical outcome.

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