Hepatic Angiosarcoma: a Review of Twelve Cases

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OBJECTIVE Hepatic angiosarcoma (HAS), a lethal disease, is the most common sarcoma arising in the liver. Little information about the epidemiology, etiology, diagnosis and management of HAS has been reported. Increased familiarity with this disease will facilitate correct diagnosis and help to improve management of this condition in the future. The objective of this study was to describe cases of hepatic angiosarcoma and to discuss the etiologic, diagnostic, therapeutic features and prognosis of this tumor. This report not only serves to give more evidence of the relationship between hepatic angiosarcoma and carcinogenic exposure, but also demonstrates the key points in different methods of diagnosis and the optimal treatment of hepatic angiosarcoma.

METHODS Twelve cases of hepatic angiosareoma were analyzed retrospectively, representing the different character in clinical presentations and laboratory computed tomographical scans; pathological data and treatment are described. Clinical and biologic follow-up was carried out for two years after surgical treatment.

RESULTS There were nine men and three women varying in ages from 57 to 71 years with an average of 64.3 years. Ten patients had a history of exposure to vinyl chloride or thorotrast. Mild or moderate abdominal pain and bloating, abdominal mass and fever were the common clinical presentations. Tumors were visualized by ultrasonography and CT scans in all patients. Biochemical profiles yielded variable results and proved to be of little value in detection or diagnosis. Surgical resection was feasible for each patient who was treated as follows: two wedge resections, six segementectomies and four bisegmentectomies. Five patients received Neoadjuvant chemotherapy postoperatively. The survival rate of those cases was poor. The maximum survival time was fourteen months. The mean survival time for this chemotherapeutic group was 11 months. The difference between the survival time of those treated with an operation plus chemotherapy versus only an operation was significant (P=0.0086, <0.05).

CONCLUSION Hepatic angiosarcoma, progressing rapidly after diagnosis, has a poor prognosis. The relationship between the development of hepatic angiosarcoma and the long period of exposure to carcinogens is presented in this report. CT imaging has some specific importance in diagnosis. The diagnosis of the lesion was dependent upon the pathologic data. Complete resection may be the only effective therapy for primary hepatic angiosarcoma at present. Better adjuvant chemotherapy is necessary to increase the survival rate of this disease.

KEYWORDS: hepatic angiosarcoma, vinyl chloride, thorotrast diagnosis, treatment.

Received July 30, 2004; accepted March 1, 2005.

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Although rare, primary hepatic angiosarcoma is the second most common primary malignant neoplasm of the liver. Worldwide, over 200 cases are diagnosed annually,[1] accounting for as much as 2% of all primary liver tumors.[2] The disease is four times more common in men compared to women,[3] the epidemiology of which reflects the relatively high rate of exposure in men to specific carcinogens including vinyl chloride, arsenic, Thorotrast and radium.[4-6] It is wellknown that hepatic angiosarcoma is an aggressive, often asymptomatic malignant disease. The prognosis is very poor with the median survival time reported to be just 6 months. Probably, because of its late presentation and the empirical nature of its treatment, hepatic angiosarcoma is a lethal disease. Currently, only 3% of the patient's survive beyond 24 months after diagnosis[6].

MATERIALS AND METHODS

The cases came to our attention through a retrospective epidemiologieal study of hepatic angiosarcoma in the same institute from 1990 to 2001. Twelve patients who had hepatic resection were included in our study. There were 9 men and 3 women varying in age from 57 to 71 with an average age of 64.3 years, (62.5 for men and 59.2 for women). The history of occupational exposure to vinyl chloride and Torotrast was reviewed for every patient. The clinical presentation and laboratory data were recorded and analyzed. Unenhanced and biphasic contrast-enhanced helical computer tomograpy was performed in all patients. Tumors were visualized by ultrasonography in all patients. The diagnosis of hepatic angiosarcoma was confirmed by pathologic findings. Hepatic resection was feasible in each patient, including 2 wedge resections, 6 segementectomies and 4 bisegmentectomies. Postoperatively, 5 patients received chemotherapy and each patient was followed-up regarding their clinical and biological features.

RESULTS

Twelve patients had developed HAS over the last ten years. Ten patients (83.3%) had a history of exposure to vinyl chloride or Thorotrast (Table 1). The mean duration exposure was 21.3 years (range 11 to 35 years) and the mean latency was 22.3 years (from 15 to 35 years) (Table 1).

Clinically, 10 of these patients were examined for abdominal bloating and pain. Seven had a slowly progressive abdominal mass. Eight of the patients had a liver that was palpable below the right costal margin

Table 1. Occupational details and survival rate of the twelve cases in this report

Case	Age at diagnosis (y)	Years of exposure (y)	Year of diagnosis (y)	Latency (y)	Survival from time of presentation (mos)
1	65	22	1990	22	4
2	57	-	1991	-	2
3	68	19	1993	18	8
4	59	11	1994	19	5
5	71	13	1996	33	7
6	66	23	1997	26	4
7*	70	32	1999	35	10
8*	59	18	2000	21	11
9*	63	-	2000	-	13**
10*	68	21	2000	18	14
11	66	35	2001	20	6
12*	59	19	2001	15	5**
Mean	64.3	18.75	-	13.25	-

*: Patients who received salvage chemotherapy; **: Patient who is living now after operation during follow-up.

and was firm, and had a smooth or concavoconvex surface. Splenomegaly was found in one patient. Five suffered from fever without infection. Two had signs and symptoms of an acute abdominal pain and anemia due to rupture of the tumor. Two patients had mild or moderate jaundice. Only 3 patients suffered from ascities. Liver function tests revealed nonspecific elevations of the serum transaminases, alkaline phosphatase, and serum total bilirubin. The serum alpha-fetoprotein was lower than normal (Table 2, 3).

Table 2. Clinical presentation in twelve HAS patients (%)

Clinical parameters	Male	Female	Mean
Number of patients	9(75)	3(25)	-
Abdominal bloating or pain	7(77.8)	3(100)	83.3
Abdominal mass	5(55.6)	2(66.7)	58.3
Fever	4(44.4)	1(33.3)	66.7
Jaundice	1(11.1)	1(33.3)	8.3
Ascites	3(33.3)	-	16.7
Hepatomegaly	6(66.7)	2(66.7)	16.7
Splenomegaly with or without pancytopenia	1(11.1)	-	41.7
Spontaneous rupture	2(22.2)	-	25.0

Table 3. Clinical and laboratory data of twelve HAS patients

Clinical parameters	Result
Platelets(10^9/L)	221.0
Serum AFP (20 μg/ml)	4.0
Serum albumin (30–55 g/L)	44.5
Serum total bilirubin (60–85 g/L)	76.5
GGT (0–50 u/L)	38.2
AST (0–42 u/L)	30.0
Hemoglobin (g/L)	81.0
Alkaline phosphatase (45–132 u/L)	156.0

AFP: alpha-fetoprotein AST: aspartate aminotransferase
GGT: γ-glutamy1transferase

The cut surface of the liver showed multifocal involvement of the right and left lobes by the angiosarcomas. Sometimes, the gritty nodules could be palpated in the sections. Tumor-induced thrombi of the portal vein were seen in six cases. Microscopically, angiosarcoma cells are bizarre and multinucleated, the liver plates are disrupted and destructed. Darkly stained clusters of Thorotrast were scattered in the tumor tissue.

An operation was performed on in each patient as follows: 2 wedge resections, 6 segementectomies and 4 bisegmentectomies. Of the 12 patients in this series, 5 were treated systemicly using combination chemotherapy with Pirarubicin + Carboplatin + 5-fluorouracil for the first time after the operation, and then with Dacarbazine + Ifosfamide for the second time. Ifosfamide + Carboplatin + Etoposide.

The mean survival from time of diagnosis to death in the 5 patients who received combination chemotherapy postoperatively was 11.5 months in contrast to the other patients whose mean survival time was 5.5 months. The survival difference between the 2 groups was significant (P=0.0086, <0.05). The survival curve of patients treated with postoperative adjuvant chemotherapy after their operation was better than that of those without chemotherapy (Fig.1).

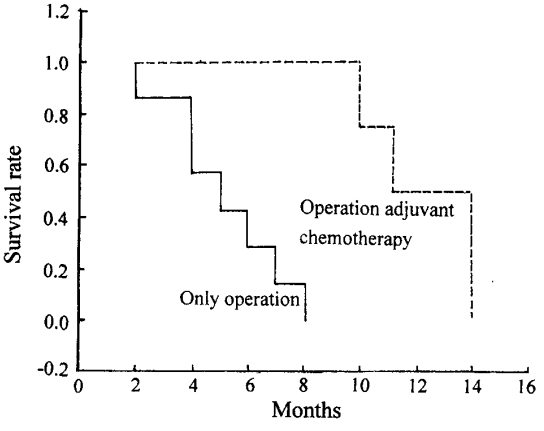

Fig.1. The survival curve for patients (n=5) treated by chemotherapy after operation in comparison with that of patients' who did not receive chemotherapy (n=7) (Kaplan-Meier method). The median survival after chemotherapy was 11.5 months, for the no-chemothrapy, 5.5 months. Difference is significant between these two groups, (P=0.0086, <0.05). Two patients treated by chemotherapy are still surviving.

DISCUSSION

Hepatic angiosarcoma, which is known as hemangioendothelial sarcoma, has been demonstrated to have a close relationship between the environment and its malignant transformation. This lesion was first report in association with exposure to Thorotrast and

arsenic, and later with vinyl chlohde by Creech and Johnson in 1974.[7-9] A survey of angiosacoma in the United States from 1964 through 1974 by Falk et al.,[10] disclosed 168 cases; 25% of those were related either to vinyl chloride, Thorotrast, inorganic arsenic or androgenic anabolic steroids. In recent published reports, it has been calculated that the background level of HAS incidence in UK is between 2 and 7 cases per year.[11] In China, HAS is also a rare disease with only a few reports on the clinical manifestations, diagnosis and treatment being published.

Clinical features

Although the relationship between the environmental exposure to some carcinogens and pathogenesis has been confirmed by recent studies, the exact pathogenic mechanisms have not, as yet, been determined. HAS may be related to environmental or other unknown factors.

The clinical manifestations of patients with hepatic angiosarcoma are generally nonspecific. Prominent symptoms are abdominal pain and bloating, abdominal mass, splenomegaly with or without pancytopenia and fever. Laboratory test results can not be used as substitutes for histological diagnosis.

Imaging studies

Radiologic evaluation included abdominal ultrasound and computed tomographic scans. Ultrasonographic results showed that angiosarcoma of liver manifested as multifocal lesions in 7 patients, and the remainder was only one of massive focus with high or mixed echogenicity. Pre-, and post enhanced identified apparent diffusely infiltrative lobular mass in these cases. These cases also showed different tumor enhancement. Six lesions were hyperdense and 4 isoattenuating on portal venous phase images. Two hypodense masses were demonstrated in the right lobe of the liver, exhibiting central contrast enhancement.

Imaging features of an angiosarcoma of the liver could be confused with those of hepatic hemangioma. So it is important to recognize the spectrum of imaging features of angiosarcoma, particularly those shown with the multiphase contrast-enhanced helical technique. Because this lesion does not display specific features in the computer tomography/scan, we should strive for a differential diagnosis among benign vascular tumors of the liver, such as the simple haemangioma and giant cavernous haemangioma, and other primary malignant tumors of the liver, including hepatocellular carcinoma, and vascular metastasis.[12] In our experience, hemangiomas display a number of features such as hypoattenuation on the pre-contrast scan, early peripheral contrast enhanced progressive opacification from periphery to center, a delay of at least 3 min before total enhancement. Giant size is shared with hepatic angiosarcoma, while the later has some CT features with other malignant liver neoplasms, which includes liver metastasis and mutifocal tumors. Hepatic angiosarcomas appear hypodense relative to normal liver prior to intravenous contrast enhancement. An initial unenhanced scan will allow easier recognition of foci of tumor enhancement later on subsequent contrasted scans. Faster scanning techniques have described typical CT findings of centripetal nodular enhancement that approximate the density of the contrast-opacified blood in the aorta or hepatic artery during all phases of imaging, including unenhanced imaging.[13]

With multiphase helical CT, the assessment of the various patterns of angiosarcoma-lesion enhancement in comparison with patterns of normal vascular enhancement, allows confident exclusion of the diagnosis of hemangioma. The pattern of progressive centripetal nodular enhancement seen with hemangioma is not typical of the patterns of enhancement scan with angiosarcoma.

Hepatic angiosarcoma has reportedly been associated with spontaneous tumor rupture and intraperitoneal hemorrhage.[14] Two of our patients had hemoperitoneum, which was confirmed by operation. This hemorrhage probably reflects the mechanism of the development of this tumor related to exposure of specific carcinogens and the vascular nature of the tumor.

Pathology

The characteristic pathologic findings provide

evidence for the diagnosis of HAS. Angiosarcoma is usually a single mass. Sometimes, the entire liver is involved. On the cut sections, the tumor tissue looks grayish-red, pale and green in colors alernating with hemorrhagic foci. Microscopically, the tumor is composed of malignant endothelial cells which can be shown by the presence of factor VIII.[15] These cells are spindle-shape or irregular in outline and have ill-defined borders. The cytoplasm is lightly eosinophilic, and nuclei are hyperchromatic and elongated or irregular in shape. Nucleoli can be small or large and eosinophilic. Large, bizarre nuclei and mutinucleated cells may be seen. Sinusoidal growth is the most common presentation and is associated with progressive atrophy of liver cells and disruption of the plates, formation of larger and larger vascular channels and eventually the development of cavity spaces of varied size. The cells involved in these tumors may be difficult to distinguish from reactive cells or they may be quite unusual showing irregular, bizarre giant cell form. Their significant relation to hepatocyte plates and obvious blood filled spaces are valuable diagnostic features.

Treatment and prognosis

Complete surgical resection should be carried out effectively and systemic salvage chemotherapy is necessary and seemed to contribute to some prolongation of survival.

The majority of patients with HAS die in less than 6 months after diagnosis, usually from liver failure, abdominal bleeding or disseminated intravascular coagulation (DIC).

In summary, patients with a history of exposure to vinyl chloride or thorotrast should be under lifelong follow-up. The optimum treatment for angiosarcoma has yet to be established, but the method of complete resection plus adjuvant chemotherapy up to now represents the best management available.

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