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Unusual presentation of hepatic vascular tumors as fulminant hepatic failure

Fulminan karaciğer yetmezliği olarak ortaya çıkan hepatik vasküler tümörler

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Epithelioid hemangioendothelioma and angiosarcoma of the liver are rare neoplasms of vascular origin. They can present with nonspecific symptoms such as malaise and weight loss, as well as with liver-related symptoms such as abdominal pain, tender hepatomegaly and jaundice. Portal hypertension and rarely liver failure can occur. We hereby report two cases offulminant hepatic failure that were eventually diagnosed with epithelioid hemangioendothelioma and angiosarcoma of the liver.

Key words: Epithelioid hemangioendothelioma, angiosarcoma, fulminant hepatic failure.

Epiteloid hemanjioendotelioma ve anjiosarkoma karaciğerin nadir vasküler orjinli tümörlerindendir. Halsizlik, kilo kaybi gibi non-spesifik semptomlar yanında ağrılı hepatomegali, karın ağrısı ve sarılık gibi karaciğere ait bulgularla presente olabilir. Portal hipertansiyon ve nadiren de karaciğer yetersizliği gelişebilir. Burada fulminant karaciğer yetersizliği ile başvuran epiteloid hemanjioendotelioma ve anjiosarkoma tanisi alan iki olgu sunuldu.

Anahtar kelimeler: Epiteloid hemanjioendotelioma, anjiosarkoma, fulminant karaciğer yetersizliği

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) and angiosarcoma (AS) of the liver are rare vascular tumors that arise from the endothelial cell lining of the hepatic sinusoids (1,2). The clinical presentation can vary from nonspecific symptoms such as malaise and weight loss to more liver-related symptoms with abdominal pain, tender hepatomegaly and jaundice. Portal hypertension and rarely liver failure can occur. Most patients remain asymptomatic and are only incidentally diagnosed (1-5). We hereby report two cases with the diagnosis of AS and EHE of the liver, who were initially referred for liver transplantation due to fulminant hepatic failure (FHF).

CASE 1

A 43-year old Caucasian female was transferred from an outlying hospital to the Liver Intensive Care Unit (ICU) of Integris Baptist Hospital, Oklahama City with acute liver failure. As per the history obtained from her family, she had been in her usual good health until three weeks prior to her hospitalization when she started to suffer from fatigue and jaundice along with increasing ascites. Diuretics were initiated by her primary care physician and she was also treated with trimethoprim/sulfamethoxazole for urinary tract infection. Ascites and jaundice persisted and she was eventually admitted to the ICU with grade III hepatic encephalopathy. She was acidotic and showed signs of renal failure, with a creatinine level of 5.3 mg/dl. She was intubated and transferred to the Liver Unit to be evaluated for orthotopic liver transplantation (OLT). Her medical history also included tubular sclerosis, hypothyroidism, and hemorrhoids. Her family reported no

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Table 1. Laboratory parameters on admission

Parameters	*Unit*	*Normal range*	*Patient 1*	*Patient 2*
Hematocrit	%	41-50	28.4	22.3
WBC	mm^3	3.8-10.8	16.4	15
Platelets	mm^3	130-400	32	43
Urea	mg/dl	7-25	107	61
Creatinine	mg/dl	0.5-1.4	5.4	1.5
Uric acid	mg/dl	2.5-6.5	11.6	NA
Glucose	mg/dl	70-125	189	142
ALT	U/L	0-48	167	132
AST	U/L	0-42	495	308
GOT	U/L	0-65	44	44
LDH	U/L	80-200	920	539
ALP	U/L	20-125	149	113
T.bilirubin	mg/dl	0.0-1.3	13.3	14
Albumin	mg/dl	3.5-5.0	2.9	1.8
PT(INR)	seconds	9-11.5(0.9-1.10)	22.4 (3.46)	26.4 (2.64)
NH3	UMOL/L	10-60	89	150
HbsAg		Negative	Negative	Negative
Anti-HBc		Negative	Negative	Negative
Anti-HCV		Negative	Negative	Negative
Anti-HIV		Negative	Negative	Negative
CMVdGM)		Negative	Negative	Negative
HSV(IGM)		Negative	Negative	Negative
EBV(IGM)		Negative	Negative	Negative
ANA		Negative	Negative	Positive (1/80)
LKM		Negative	Negative	Negative
SMA		Negative	Negative	Negative
AMA		Negative	Negative	Negative
_lpha fetoprotein	ng/ml	<8.5	5.7	3.6
CEA	ng/ml	Nonsmoker<2.5		
Smoker<5.0	14.5	4.3		

exposure to toxic substances, intravenous drug use, oral contraceptives, alcohol, smoking, or history of previous liver disease. She had no tattoos.

Upon admission, the patient had jaundice, ascites and grade IV hepatic encephalopathy. She was responsive only to painful stimuli. Her blood pressure was 104/40mmHg, pulse 92/min, temperature 35.6^{S}C, and her weight was 106kg. She had no spider angioma and palmar erythema. The liver was palpated 1cm below the costal margin and there was no splenomegaly. The chest examination revealed some rhonci and diminished breath sounds in the lower lobes. Her laboratory test results are summarized in table 1. Abdominal ultrasonography (US) showed enlarged, heterogeneous liver with a mass (3.2cmx2.4cmx2.4 cm) in the inferior right lobe. Moderate amount of ascites was also noted. Abdominal computerized tomography (CT) with intravenous contrast showed ascites, minimal pleural effusion and a diffusely heterogeneous, nodular liver. Some of the nodules measured up to 2cm in diameter. The spleen was normal. It was thought that this picture might be consistent with metastatic disease. At that point, after correction of coagulopathy with plasmapheresis, percutaneus liver biopsy was performed. Histology of the liver revealed a vascular tumor, consistent with epithelioid hemangioendothelioma. Its vascular origin was confirmed by immunoperoxidase stain with factor VHI-related antigen. Cytokeratin, a-fetoprotein, epithelial membrane antigen (EMA), leukocyte common antigen (LCA) and viral markers (CMV, Herpes, Hepatitis B) were negative. Serum level of the alpha-feto protein was within normal limits.

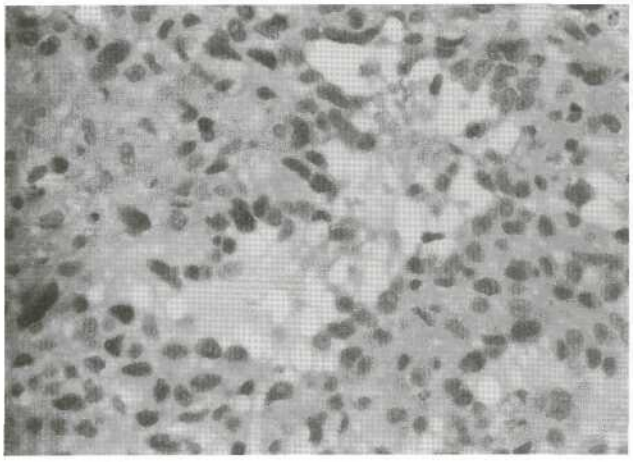

Figure I. Vascular spaces revealing malignant transformation of endothelium.

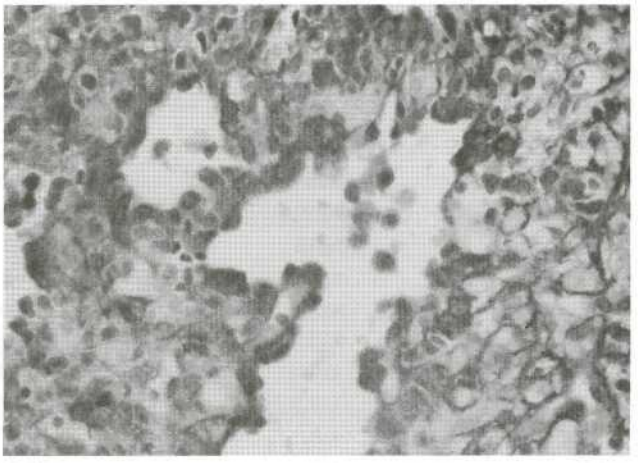

Figure 2. Strongly positive Factor VII-Related Antigen by immunoperoxidase.

Serum carcinoembryonic antigen (CEA) was slightly high. Hepatic arteriogram was performed which showed non-specific findings. Her condition continued to deteriorate with progressive renal and hepatic failure and she eventually died of multiorgan failure on day six of hospitalization. Autopsy was not performed at the family's request.

CASE 2

A 39 year-old white female was referred for evaluation for OLT with FHF. She had developed fatigue, jaundice, myalgia, low-grade fever and anasarca a week prior to her admission. She had a low serum albumin of 1.8mg/dl, high serum total bilirubin of 4.6mg/dl and elevated prothrombin time of 20.4 (INK of 2.03) seconds. The serology for hepatitis B surface antigen, B antibody and hepatitis C antibody were negative. Antinuclear antibody (ANA) was slightly positive at 1:80 titer. Serum alpha feto protein was within normal limits, while CEA was slightly high. At that point she was transferred to the Liver Transplant Unit for further evaluation and treatment. No significant past history was present. She reported no intravenous drug or alcohol use, tattoos, smoking or oral contraceptive use.

Upon admission, she was alert and had mild respiratory distress. Her blood pressure was 154/60 mmHg, pulse 117/min, respiratory rate 30/min and temperature 36.9°C. Her weight was 143.6 kg and height 1.63 meters. Chest examination revealed rales in all lobes. She had generalized edema and jaundice and the liver and spleen could not be examined because of her obesity. She was intubated on the first night of admission. Her laboratory values are summarized Table 1.

Abdominal US and CT with IV contrast injection both showed marked hepatomegaly with diffuse increase in echogenicity, without evidence of any liver mass. There was no ascites or splenomegaly. The portal vein was enlarged, while the hepatic veins and inferior vena cava were normal. Transjugular liver biopsy was performed after plasmapheresis and histology revealed angiosarcoma (Figure 1). Factor VIII related antigen was strongly positive using immunoperoxidase stain (Figure 2) but LCA, EMA and CD34 were negative. Liver transplantation was not an option. Despite intensive medical supportive care she died seven days after admission to the Liver ICU due to multisystem organ failure. Autopsy was not performed at the family's request.

DISCUSSION

Epithelioid hemangioendothelioma and AS of the liver are rare neoplasms of vascular origin. Their true incidence are not well known. Unlike AS of the liver, which is associated with chronic exposure to thorotrast, vinyl chloride, arsenic and radium (2,3,6), the etiology of EHE remains obscure (1,4,5). However, there are a few reports of EHE associated with oral contraceptive drug usage (4,5). Angiosarcoma occurs four times as

often in men as in women, while EHE, in contrast, usually affects women.

The most common initial complaint of vascular tumor of the liver is abdominal pain and/or discomfort, which is followed by malaise, fever, weight loss, nausea, jaundice and progressive liver failure. Some patients are diagnosed incidentally. The laboratory data are usually nonspecific except for elevated serum alkaline phosphatase in approximately 75% of all patients. Tumor markers such as oc-feto protein, CEA, CA19-9 are usually not elevated (1-5,7).

Both of our patients were referred for liver transplantation because of hepatic encephalopathy, progressive jaundice, coagulopathy and edema. They had no previous history of liver disease and had been in their usual good health. There were no stigmata of chronic liver disease. Fulminant hepatic failure in both patients were diagnosed by hepatic encephalopathy and other manifestations of liver cell failure in the absence of pre-existing liver disease, fulfilling the criteria as defined by O'Grady et al (8). The cause of death in both patients was multiorgan failure, renal failure, acute lung injury and liver failure, all occurring within one week of hospitalization. The mechanism of malignancy advancing into FHF is unclear. Rowbotham et. al (9) suggested FHF to be due to tumor infiltration of the biliary tract, hepatic parenchyma and hepatic vasculature. Infiltration of bile ducts results in severe cholangitis, duct necrosis and FHF. Obstruction of hepatic and portal venules by tumor may also result in hepatic ischemia and subsequent hepatocellular necrosis. Rapid invasion of hepatic parenchyma by tumor mass may lead to destruction of critical hepatocyte mass, subsequently causing FHF. Obliteration of hepatic vasculature and rapid growth of tumor cells may have resulted in hepatocellular necrosis and FHF in our cases also. To our knowledge, presentation of primary hepatic malignancy with FHF is extremely rare (10). One case of malignant hemangioendothelioma of the liver leading to FHF has been reported in the literature (11).

The prognosis of AS of the liver is extremely poor, most cases dying within a few months (2). Neither resection of liver mass nor transplantation (15) are practicable due to the high rate of recurrence and metastases and it is not responsive to either radiotherapy or chemotheraphy (2,3). Various kinds of treatment for EHE have been reported, such as OLT, resection, chemotherapy and radiotherapy (4,5,12-14). Because of the inability to predict the behavior of this tumor, it is impossible to elucidate which treatment is most effective. Comparing the prognosis of EHE of the liver with primary AS, there is no doubt that the former has a significantly better outcome.

Neither of our patients had exposure to carcinogens or a history of oral contraceptive use. Their initial symptoms were nonspecific, followed by jaundice, ascites and edema. They rapidly deteriorated into FHF with death occurring within one week of admission, despite prompt medical supportive treatment. Liver transplantation was not performed in either case.

There are no specific clinical or biochemical features to differentiate between the various other causes of FHF and hepatic malignancy. In a patient presenting with FHF of no apparent cause, the possibility of hepatic malignancy should also be considered. Obviously, liver biopsy performed by either the percutaneous or transjugular approach, plays a most crucial role in confirmation of diagnosis.

Computerized tomography and US appearances of AS and EHE of the liver are nonspecific. They usually present as multiple nodular lesions involving both lobes of the liver, consistant with a vascular tumor lesion. The differential diagnosis should include benign vascular tumors, hepatocellular carcinoma, and vascular metastases (4,5,16). MRI scans and angiography of these tumors are highly specific, but the final diagnosis relies upon the demonstration of cells containing FVIII-Related Antigen in the liver tissue. Due to vascularity, the tumor and associated thrombocytopenia and coagulopathy, a transjugular liver biopsy can be considered as more advantageous compared to the percutaneus approach.

In conclusion, diffuse involvement of the liver with malignant vascular tumors may result in FHF and a history of exposure to specific carcinogens is not necessary for the diagnosis. Differential diagnosis between EHE and AS of the liver is important before consideration of OLT, because OLT is absolutely contraindicated in the latter. In contrast, OLT should be considered in some selected cases of EHE, because there is a higher chance of achieving a meaningful survival.

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