Primary Malignant Hepatic Epithelioid Hemangioendothelioma: Case Report and a Comprehensive Review of the Literature

Primer Malign Hepatik Epiteloid Hemanjioendotelyoma: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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ABSTRACT Hepatic epithelioid hemangioendothelioma (HEH) is a vascular originated, low grade malignancy, generally seen in soft tissues and visceral organs, and its incidence is very low. Although HEH is a low grade tumor; its clinical outcome and prognosis may differ. In some patients it progresses aggressively and ends up with the patient's death in a few months; in others long term survival can be observed. Our patient who is a 55 years old woman, was referred to our clinic with right upper quadrant pain and we established HEH diagnosis on her. This case was represented in order to emphasize that HEH should be taken into account in differential diagnosis in vascular originated lesions of liver.

Key Words: Hemangioendothelioma; liver neoplasms; immunohistochemistry; therapy

ÖZET Hepatik epiteloid hemanjioendotelyoma (HEH) vasküler orijinli, genellikle yumuşak dokuları ve visseral organları tutan, düşük gradeli bir malignite olup, ve oldukça nadir görülmektedir. HEH düşük gradeli bir tümör olduğu halde klinik bulguları ve prognozu açısından değişik seyredebilmektedir. Bazı hastalarda oldukça agresif seyredip birkaç ay içinde ölümle sonuçlanırken bazı hastalarda ise oldukça uzun yıllar sağkalım gerçekleşmektedir. Karın sağ üst kadran ağrısı şikayeti ile kliniğimize başvuran 55 yaşındaki kadın hastamıza HEH tanısı koyduk. Bu olgu, karaciğerin vasküler orijinli lezyonların ayrıcı tanısında HEH'in göz önünde bulundurulması gerekliliğini vurgulamak için sunulmuştur.

Anahtar Kelimeler: Hemanjioendotelyoma; karaciğer tümörleri; immünohistokimya; tedavi

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Epithelioid hemangioendothelioma (EH) is a rare neoplasm of vascular origin that involves soft tissues and visceral organs.[1] The term EH was defined as a distinct entity by Weiss and Enzinger as a soft tissue vascular tumor of endothelial origin with a clinical course between benign hemangioma and angiosarcoma.[2] Primary malignant hepatic EH (HEH) is a rare tumor with an incidence of <0.1 per 100.000 population and seen in a wide age range, generally in women.[1] Pathological features are characterized by an epithelioid or histiocytoid morphology and a growth pattern with evidence of endothelial histogenesis. Its vascular nature is confirmed by positive staining for factor VIII-related antigen and other endothelial cell markers such as CD31 and CD34. Liver resection (LR), liver transplantation (LT), chemotherapy (CTx), and/or im-

munotherapy have been used in the treatment.[1,3] In our article; we present a fifty five years old woman with multiple nodular liver lesions and a pathologic diagnosis of tru-cut biopsy compatible with HEH. Because of the coexistence of nodular lung opacities the lesion was accepted as metastatic HEH. Patient was given thalidomide 400 mg/day. The patient's follow-up still continues.

CASE REPORT

Fifty five years old woman who has hypertension and diabetes mellitus, referred to our clinic with right upper quadrant pain that started two months ago. In patient's physical examination; hepatomegaly was found and other system examinations were normal. Patient's abnormal laboratory findings were high alanine aminotransferase (ALT: 59 U/L) and aspartate aminotransferase (AST: 27 U/L) levels and low total biliuibin level (0.36 g/dL). In ultrasonography; multiple hepatic masses were seen in all segments of liver. The largest mass (7 cm in greatest diameter) was located in the right lobe (Figure 1a-1b). The borders of the nodules were irregular and dense nodular calcifications were seen. Multislice computed tomography (CT) revealed peripheral type contrast enhancement in early arterial phase and also in all dynamic series. Lesions did not make irregularity or lobulation in liver contours; but in some sections in liver parenchyma especially in peripheral region; retractions were seen (Figure 2a-2b). In magnetic resonance imaging (MRI); in T1 dominant sequences hypointens and in T2 dominant sequences hyperintense characteristics were shown. After contrast injection, from arterial phase through the peripheral phase, large

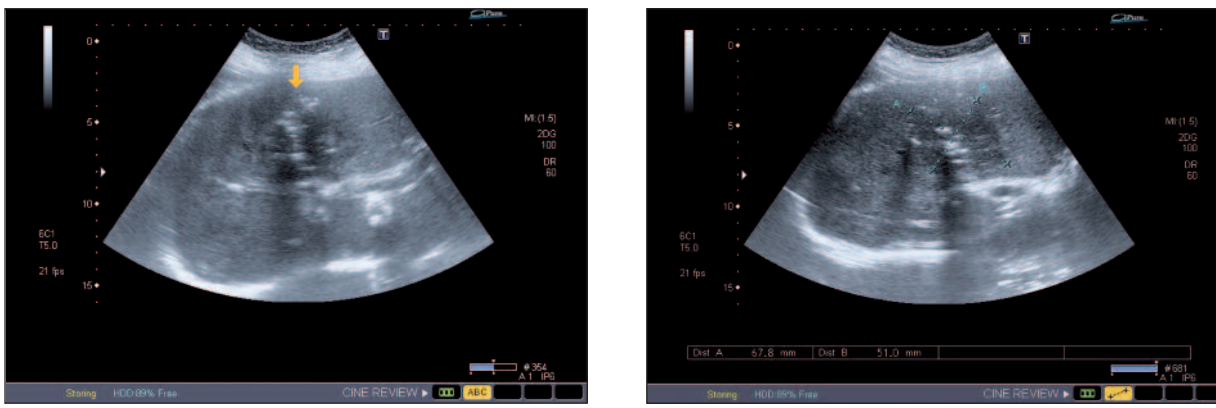

FIGURE 1a-1b: In liver right lobe; up to 7 cm diameter, irregular contoured and consist of dense nodular calcifications; multiple hypoechoic mass lesions.

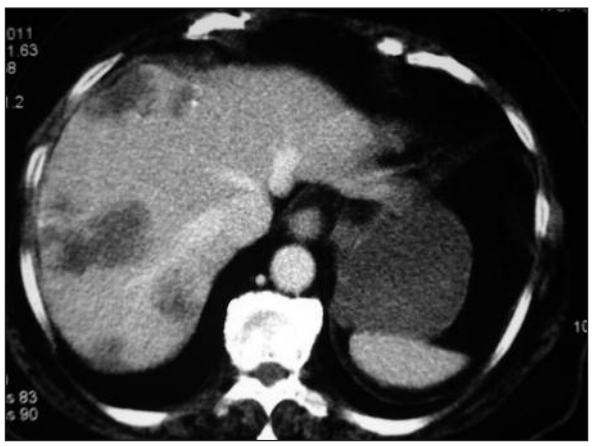

FIGURE 2a: In liver approximetly 5 cm diameter irregular contoured, consist of calcifications in some regions, multiple hypodense lesions.

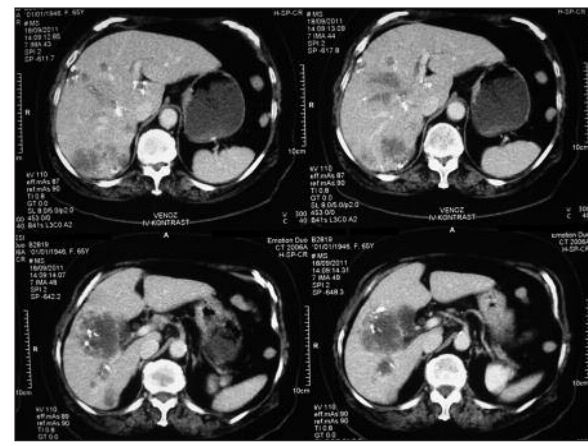

FIGURE 2b: Dynamic contrasted series taken after IVKM ; peripheral contrasting in arterial phase.

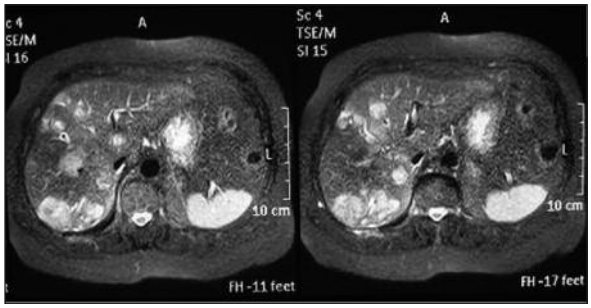

FIGURE 3a: In T2 dominant axial sections; irregular contoured marked hyperintense lesions.

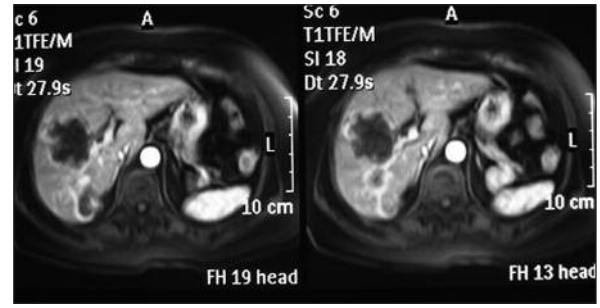

FIGURE 3b: Axial imaging after IVKM; peripheral type marked contrasting.

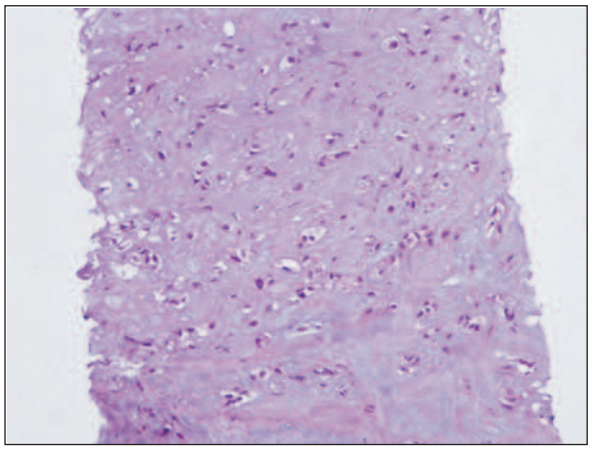

FIGURE 4: Inside desmoplastic stroma; tumor cells changing from smaller to bigger size which are spreading through vessels (H&E x100).

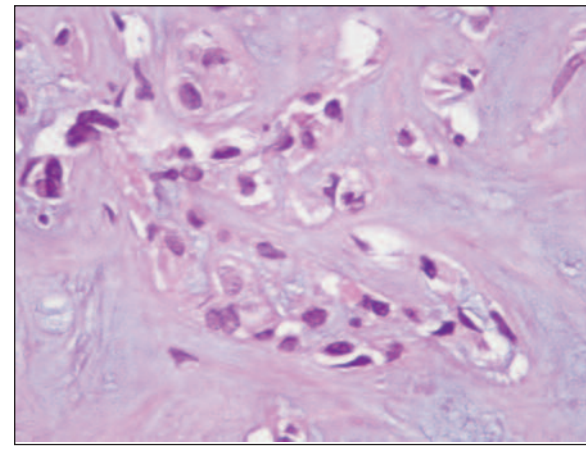

FIGURE 5: Tumor cells have middle grade nuclear atypia and cytoplasmic vacuoles which include erythrocytes (H&E x400).

number of irregular contoured mass lesions contrasted. Lesions resume peripheral contrasting in late lesions and central regions did not enhance contrast (Figure 3a-3b). In addition a few nodular opacities (1 cm in greatest diameter) were identified in both lungs by thoracic CT. Tru-cut biopsy was performed. Microscopic examination revealed tumor cells proliferating around the sinusoids in desmoplastic stroma (Figure 4). The high proportion of proliferating cells were small and had an epithelioid morphology. Some of the tumor cells were spindle-shaped. Mild to moderate nuclear atypia were seen and some of the tumor cells exhibited cytoplasmic vacuoles and inside those vacuoles erythrocytes were observed (Figure 5). Mitotic activity and necrosis, which are characteristics of an angiosarcoma, were not found. Neoplasm cells did not react with epithelial marker pancytokeratin, so a carcinoma was excluded. But tumor cells exhibited strong and diffuse positive reaction with mesencymal markers such as vimentin and endothelial markers such as CD34 (Figure 6), CD31 and Factor VIII related antigen. The morphologic appearance

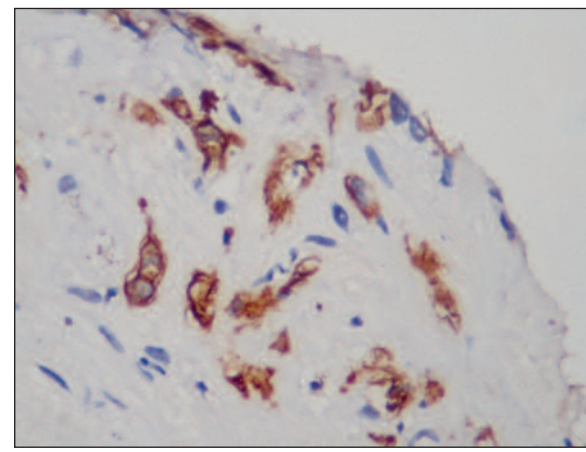

FIGURE 6: CD 34 positiveness of tumor cells (CD34 x400).

and endothelial immunophenotype were compatible with HEH. Because of the concominent pulmonary lesions, the patient was considered to have a metastatic disesase. Patient was given thalidomide 400 mg/day. The patient's follow-up still continues.

DISCUSSION

HEH is a rare neoplasm of vascular origin with an incidence of <0.1 per 100 000 population and seen in a wide age range, generally in women. Its etiology is unknown but oral contraceptive use, vinyl chloride and silicon exposure, primary biliary cirrhosis, hepatitis B infection and major trauma are thought to be etiological factors. The mean age of patients with HEH is 41.7 years, and the male to female ratio is 2:3.[1] One quarter of the patients are detected incidentally. In symptomatic cases; right upper quadrant pain (48.6%), hepatomegaly (20.4%) and weight loss (15.6%) are major symptoms[4]. Most patients presented with multifocal tumor that involved both lobes of the liver. Lung, peritoneum, lymph nodes, and bone were the most common sites of extrahepatic involvement at the time of diagnosis[1] (Table 1 summarizes the patients' initial metastasis status and treatment datas avaliable). Laboratory findings are not helpful for diagnosis because tumor markers like CEA, CA 19-9 and alpha fetoprotein (AFP) levels can be in normal limits. But in advanced stages of the disease; jaundice, abdominal pain and abnormal liver function tests can be observed.[5]

Ultrasonographically (USG), a great number of hypoechoic irregular bordered nodular lesions or diffuse heterogeneous view of liver parenchyma attracted attention. Furui et al. classified HEH into two groups; nodular and diffuse. Nodular lesions are early forms of HEH and it is reported that this form can turn into diffuse type later. Radiological findings of diffuse type can be typical for HEH but nodular form can be mixed with especially metastasis and many other lesions.[6] In USG; separate nodules or a heterogeneous structure may be seen in liver parenchyma. Lesions are generally hypoechogenic but they can also be iso or hyperechogenic according to the liver parenchyma.[7] In CT; lesions are generally located peripherally and enlarge the liver capsule. In 25% of the patients; retraction is observed in the liver parenchyma adjacent to the neoplasm. Earnest and Johnson, thought that; this finding is the most important diagnostic characteristic and it is useful for radiologists in differential diagnosis of HEH and other neoplasms.[8] On the other hand; hepatic parenchyma calcification is a common finding too. In contrasted CT; lesions are peripherally contrasted in arterial phase and central parts are hypodens. But sizes of the lesions can be understood most accurately in images without contrast.[9] In MRI; lesions are more hypointense than liver parencyhma in T1 predominant images and heterogeneous or hyperintense in T2 predominant images. Lesions pick up contrast in the periphery or in a target pattern in contrasted images after gadolinium and central parts can be hypointense because of coagulation necrosis, calcification or hemorrhage. Settling in liver periphery and retraction findings in parenchyma are the most likely findings in CT.[8,9] In our case; USG, CT and MRI findings of the lesions were similar with literature and settling in periphery and liver retraction charecteristics caused suspicion of a typical liver malignancy but because of its contrast characteristics hemangioma was not considered.

Pathological features of HEH are characterized by an epithelioid or histiocytoid morphology and a growth pattern with evidence of endothelial histogenesis. Neoplastic cells typically invade liver sinusoids, and finally marked parenchymal atrophy develops. Desmoplastic stromal response is marked especially in the tumor center.[1] Immunocytochemically; HEH cells react with vimentin, and endothelial markers such as factor VIII related antigen, CD31 and CD34.

Approximately 60% to 80% of patients with HEH were initially misdiagnosed.[10-12] The most common misdiagnoses were angiosarcoma, cholangiocarcinoma,hepatocellular carcinoma (HCC), metastatic carcinoma.[10] Major differential diagnosis is with angiosarcoma but angiosarcoma is characterized with irregular vascular channels that can include solid or pseudopapillary structures, and differs from HEH with high grade nuclear atypia,

TABLE 1: Patients' initial metastasis status and treatment datas avaliable evaluated for hepatic epithelioid hemangioendothelioma from 1993 to 2012.

Author	Number of cases	Initial Metastasis	Treatment
Agrawal[17]	4	Nil	LT
Harada[18]	1	Nil	TACE
Salech[19]	1	Lung	CTx
Raphael[20]	1	Lung	CTx
Grotz[3]	30	Lung (8), Peritonium (2), Bone (2), Skin (1), Brain (1)	LT (11), LR (11), CTx (5), Obs (3)
Chang[21]	1	Nil	CTx
Hsies[22]	6	Nil	LT (2), Obs (4)
Kanizaj[23]	1	Nil	LT
Guiteau[24]	35	Not mentioned	LT
Thin[25]	5	Nil	LT (1), Obs (4)
Hansova[26]	6	Lung (2)	LT (6)
Tonglet[27]	1	Nil	LT
Jeong[28]	1	Nil	LR
Oshima[29]	1	Nil	LR
Öztürk[30]	1	Nil	LR
Cardinal[31]	25	Lung (3), Bone (1), LN (2), Omentum (1), Chest wall (1)	LT (19), TACE (4), LR (2)
Nudo[32]	11	LN (2), Spleen (1)	LT (11)
Masoia[33]	9	Nil	LT (6), LR (3)
Bufton[34]	3	Nil	LT (3)
Garcia-Botella[35]	2	Nil	LT (1), LR (1)
Mucha[36]	1	Nil	LT
Akça[37]	1	Nil	LT
Langrehr[12]	6	Nil	LT (2), LR (3), CTx (1)
Lerut[38]	5	Nil	LT (5)
Madariaga[39]	17	Lung (1)	LT (17)
Debernardi[40]	1	Nil	LT
Sharif[41]	5	Nil	LT (6), CTx(1)
Mehrabi[1]	5	Nil	LT (3), Obs (1), LR (1)
Fedeli[42]	2	Nil	LT (1), Obs (1)
Bancel[43]	1	Nil	LT
Our case	1	Lung	CTx

LT: Liver transplantation; TACE: Transcatheter arterial chemoembolization; CTx: Chemotherapy; Obs: Observation; LR: Liver resecrion; LN: Lymph node.

brisk mitotic activity and necrosis.[13] Immunohistochemical identification of endothelial markers is helpful in differantiating metastatic carcinoma from primary epithelial liver tumors.[14]

In their comprehensive review Mehrabi et al. established that 77% of the patients who underwent liver transplantation (LT) were alive at a mean follow-up of 45 months. After liver resection (LR), the survival rate was 95% for all patients, with a mean observation time of 38 months The overall percentage of patients who remained alive, whether they received any kind of treatment or no treatment, was 83.4%, 55.8%, and 41.1% after 1 year, 3 years, and 5 years, respectively. The surgical therapies, LT and LR, had the best survival rates with 5-year survival rates of 54.5% and 75%, respectively. The survival rates decreased markedly to 30% and 4.5% for patients who received chemotherapy (CTx) or radiotherapy (RTx) and patients who with no treatment, respectively. Among the patients who received CTx or RTx, 58% remained alive at a mean follow-up of 43 months, and 42% died with a mean follow-up of 26 months. Forty percent of the patients who did not receive

any kind of treatment remained alive after a mean follow-up of 32 months; however, 60% of patients died after mean follow-up of 8 months. In this regard, HEH has unpredictable natural course and prognosis.[1] Mehrabi et al. suggest a treatment algorithm according to the presence of extrahepatic spread and involvement of liver being diffuse or not. In hemiliver involvement; if there is no extrahepatic spread LR is sufficient for treatment, whereas in extrahepatic spread LR and/or CTx or transcatheter arterial chemoembolization (TACE) and/or CTx should be applied. If liver involvement is diffuse and there is no extrahepatic spread LT should be applied while in the presence of extrahepatic spread LT and/or CTx or TACE and/or CTx should be applied (Treatment algorithm was shown in Figure 7).[1,5,7,14]

In our case since liver involvement was diffuse and extrahepatic spread was present LR was not appropriate for treatment and because we were not able to apply LT in our center, CTx was considered as the appropriate treatment choice. There are some cases reported that anti-angiogenic agents can be helpful in HEH treatment. Bevacizumab, thalidomide and low dose weekly taxane usage are the options.[15,16] In our patient; possible side effects were taken into account and thalidomide 400 mg/day treatment was started.

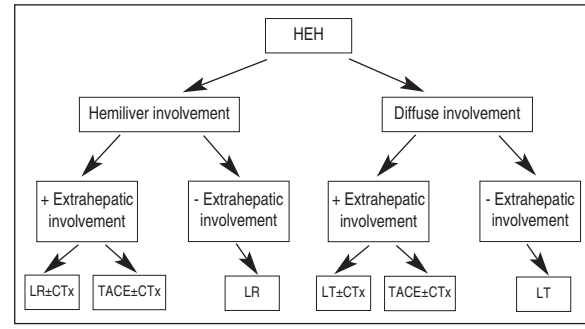

FIGURE 7: Treatment algorithm of hepatic epithelioid hemangioendothelioma (HEH).[1]

In conclusion, HEH is a very rare tumor, can be asymptomatic and does not have specific laboratory findings. Its diagnosis is difficult and rate of misdiagnosis is high. Radiologicaly, liver contour retraction, peripheral contrasting in arterial phase and calcification are important diagnostic clues. And these findings should remind us HEH in the differential diagnosis vascular lesions of liver. Because of the variable patterns of the tumor, which may mimic other lesions, the pathologist's awareness is essential.

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