Turk J Gastroenterol 2002; 13 (4): 221-225

# Hepatic epithelioid hemangioendothelioma treated with orthotopic liver transplantation : a case report

## Ortotopik karaciğer nakli ile tedavi edilen hepatik epitelioid hemangioendothelioma: Bir olgu sunumu

Serdar AKÇA[1], İnci SÜLEYMANLAR[1], Dinç DİNÇER[1], Alper DEMİRBAŞ[2], Tekinalp GELEN[3], Alihan GÜRKAN[2], Özlem ELPEK[3], Can ÖZKAYNAK[4], Fahri IŞITAN[1]

*Akdeniz University School of Medicine, Departments of Gastroenterology[1], Surgery[2], Pathology[3] and Radiology[4], Antalya*

*Hepatic epithelioid hemangiendothelioma is a rare vascular tumor. The clinical course is unpredictable and different treatment modalities are offered depending on the patients condition. Orthotopic liver tranplantation is the choice of treatment in diffuse cases without metastases. A 32 year old woman was admitted to hospital with multiple mass lesions diagnosed by ultrasonography of the liver. Physical examination was normal except for a painless hepatomegaly, and her biochemical tests were within the normal range. Computed tomographic scanning showed the presence of multiple lesions in both lobes, some of which were accompanied by a small degree of calcification. Although these findings were suggestive of hepatic epithelioid hemangioendothelioma, ultrasonographic guided fine needle aspiration biopsy failed to diagnose the exact nature of the lesions. The diagnosis of hepatic epithelioid hemangioendothelioma was confirmed by diagnostic laparotomy and immunohistochemical examination of the specimen by FVIII-RAg, CD34 and CD 31 markers. The patient was treated by orthotopic liver transplantation and had no evidence of tumor 18 months after transplantation. The problems in differential diagnosis and treatment options are discussed in this report of the first case of this rare tumor, treated by orthotopic liver transplantation in Turkey.*

Key words: Hepatic epithelioid hemangioendothelioma, diag nosis, orthotopic liver transplantation.

*Hepatik epitelioid hemangioendothelioma nadir görülen vasküler bir tümördür. Hastalığın klinik seyrini önceden tahmin edebilmek mümkün değildir. Hastanın mevcut bulgularına göre önerilen farklı tedavi yöntemleri vardır. Otuziki yaşındaki kadın olgu ultrasonografi ile teşhis edilen karaciğerdeki multiple kitleler nedeniyle araştırıldı. Fizik muayenesinde ağrısız bir hepatomegali dışında patolojik bulgu tespit edilmedi. Biyokimyasal değerler normal bulundu. Bilgisayalı tomografi ile kitlelerin bir miktar kalsifikasyon içerdiği ve tüm karaciğer segmentlerinde yaygın olduğu izlendi. ince iğne aspirasyon biyopsisi ile histopatolojik tanı konulamadı. Diyagnostik laparotomi ile karaciğerden alınan biyopsi materyali immunohistokimyasal FVIII R-Ag, CD34 ve CD31 markerları ile boyanarak hepatik epitheliod hemangioendothelioma tanısı kesinleştirildi. Hastaya kadavradan karaciğer nakli gerçekleştirildi. Nakilden 18 ay sonra olgu halen iyi durumda ve herhangi bir tümör bulgusu yoktu. Tartışmada ayırıcı tanı ve tedavi seçenekleri irdelendi. Türkiyede ilk kez karaciğer nakli ile tedavi edilen hepatik epitelioid hemangioendotheliomah olguyu bildirmekteyiz.*

Anahtar kelimeler: Hepatik hemanjiyoendotelioma, karaciğer nakli.

## INTRODUCTION

Epithelioid hemangioendothelioma is a rare vascular tumor with unpredictable malignant potential. It was first described as a distinct entity by Weiss and Enzinger in 1982 (1). The tumor was later reported in virtually all sites including lung, soft tissue, and bone (2-3). It occasionally develops in the liver, primary involvement of the liver first being reported by Ishak et al. in a series of 32 patients (4). Since then more than 260 cases have been reported. The clinical course and treatment modalities as reported in the literature are variable (4-23). In this report, the first case of hepatic epithelioid hemangioendothelioma (HEH) treated by orthotopic liver transplantation in Turkey is presented, The problems in differential diagnosis and other treatment options are also discussed.

**Address for correspondence:** Dr.Serdar AKÇA
Akdeniz Üniversitesi Tıp Fakültesi, Gastroenteroloji Bilim Dalı
Dumlupınar Bulvarı, Antalya
Tel: 0242 2274343 Fax:0242 2278202
e-mail: serdar@med.akdeniz.edu.tr

**Manuscript received:** 10.1.2002 Accepted: 12.11.2002

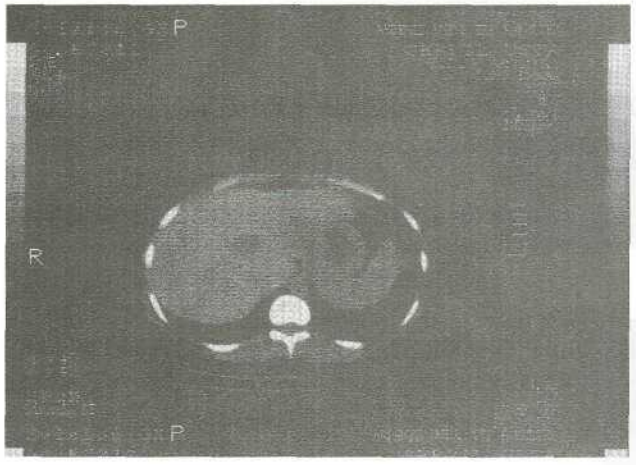


**Figure I.** Multiple mass lesions occupying liver paranchyma in computerized tomography.

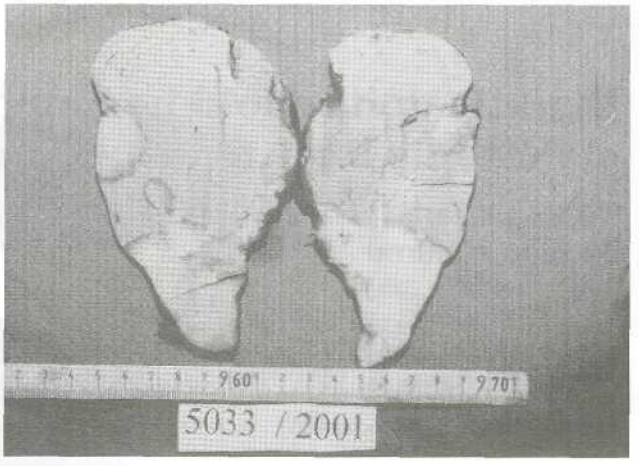


**Figure 2.** Macroscopic view of the liver.

## CASE REPORT

A 32-year-old woman was referred to our hospital with multiple hepatic lesions. She had a six-month history of right upper abdominal fullness sensation. Physical examination was normal except for a painless hepatomegaly, while laboratory findings included the following: aspartate aminotransferase: 19 U/L (normal, 10-40); alanine aminotranferase: 20 U/L (normal 0-40); gamma-glutamyl-transpeptidase: 45 U/L (normal, 0-50); alkaline phosphatase: 107 U/L (normal, 53-128); albumin: 4.3 g/dl (normal, 3.5-5); bilirubin, 0.4 mg/dl (normal, 0.2-1); alpha-fetoprotein: 2.5 lu/ml (normal, 0.5-5.5) and carcinoembryonic antigen: 1.2 mg/ml (normal 0-2.5 ng/ml). HBsAg and anti HCV were negative. Ultrasonographic examination of the liver showed hepatomegaly (200 mm in vertical diameter) with multiple hypoechoic solid masses. The portal vein and spleen were within normal limits. No esophageal varix was found on upper gastrointestinal endoscopy. Computed tomographic scanning showed the presence of multiple masses in both lobes, some of which were accompanied by a small degree of calcification (Figure 1). The thorax and other abdominal structures were normal. Fine needle aspiration biopsy was performed twice under ultrasonography guidance but malignant tissue was not found on histologic examination. A diagnostic laporotomy with hepatic wedge biopsy was performed under general anesthesia. Macroscopically the whole liver was invaded with a rubbery and a greyish-white colored tumor (Figure 2). Microscopically, the tumor had a high cellular growth pattern with infiltrative margins, but the portal tracts were well preserved despite extensive infiltration by the tumor (Figure 3). The neoplastic cells were epithelioid, shown by immunohistochemical markers of FVIII-RAg, CD34 and CD31 (Figure 4). After the definitive diagnosis of HEH without metastases, liver transplantation was planned for the patient. Orthotopic liver transplantation was performed in April 2001 and six months later there was no evidence of tumor presence.

## DISCUSSION

HEH is a rare neoplasm of vascular origin. Our case presented with a six-month history of right upper abdominal fullness, and had a normal biochemical profile. The clinical manifestations of HEH are nonspecific and variable, ranging from complete absence of symptoms to hepatic failure. In general, the clinical course is intermediate between hemangioma and hemangioendotheliosarcoma. It usually presents multifocally with few clinical signs and few biochemical abnormalities. Patients have reported nonspecific symptoms such as right upper quadrant or epigastric pain, weight loss and weakness. Less common symptoms at initial presentation are jaundice, fever and fatigue. Raised levels of serum alkaline phosphatase are found in 70% of patients, serum AFP is elevated in a minority and no raised levels of CEA are reported (4-9).Thus the clinical presentation of HEH is nonspecific and imaging techniques are important in the diagnosis. The presence of

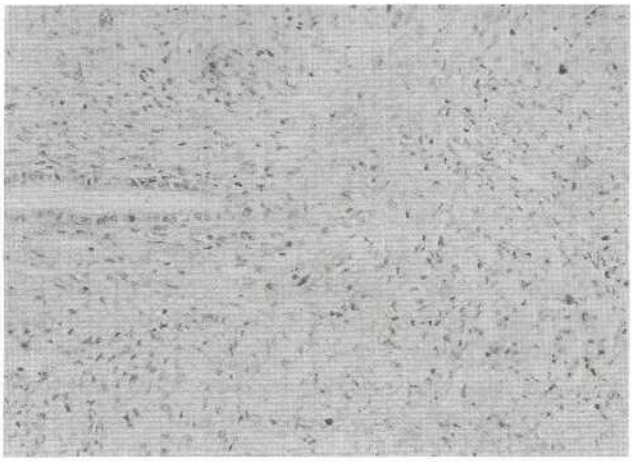

**Figure 3.** Histopathology of the liver shows portal area and tumor cells (H&E X 20).

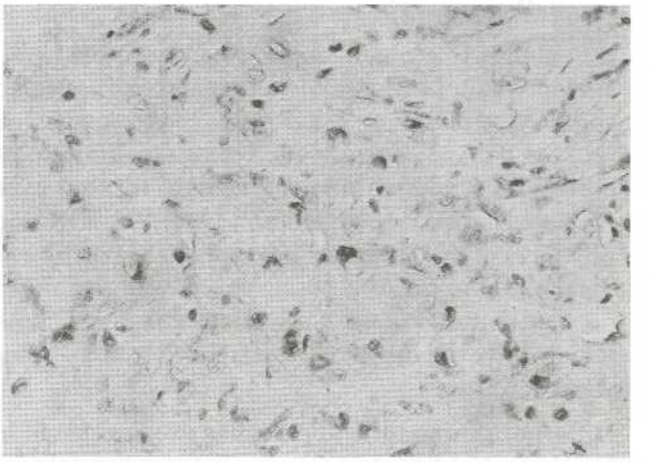

**Figure 4.** Appearence of CD-31 positive tumor cells X 40.

multiple hepatic masses diagnosed either by USG and/or CT is the most common general finding in the literature. In our case ultrasonographic examination revealed hepatomegaly and multiple hypoechoic masses in the liver greguring further investigation. The ultrasonographic findings of the vascular tumor, HEH, are non specific and it is possible to misdiagnose as metastatic carcinoma or Budd-Chiari syndrome (10,11). In the CT scan, however, there are a number of findings suggestive of diffuse HEH: the presence of a large tumor of the liver mainly located in the periphery, indentation of the liver capsule due to its fibrotic structures, peripheral enhancement of the contrast medium, as well as demonstration of hypervascularized central lesions, a tendency of the tumor nodules to merge into each other and compensatory hypertrophy of the unaffected liver segments (12-14). Our CT scan findings were very consistent with the findings in the literature, thus the most probable diagnosis was HEH although the differential diagnosis of angiosarcoma or cholangiocarcinoma and possible metastatic lesions were all considered.

For the definitive diagnosis we performed ultrasonographic guided fine needle aspiration biopsy twice. However, malignant tissue was not found on histologic examination of the two samples of aspirated material. In the literature there are reports of several cases of HEH diagnosed by immunohistochemical examination of the fine needle aspiration biopsy material (5,18), but in the majority of the cases it was diagnosed by wedge biobsy or hepatectomy (6-15). On pathological examination, the tumor was defined to have a high cellular growth pattern with infiltrative margins and preserved portal areas. The neoplastic cells were epithelioid and had an eosinophilic cytoplasm and vesicular nuclei. Histologically, HEH may mimic other vascular tumors and metastatic carcinomas. As a primary liver tumor it may cause diagnostic difficulties for the pathologist due to the pleomorphism of the tumor cells and the possible presence of paranchymal cells and a stromal reaction. Cases of HEH have been misdiagnosed as cholangiocarcinoma, fibrolamellar hepatocellular carcinoma, sarcoma and metastatic carcinoma (1,4). HEH also has been confused with venoocclusive disease because of its tendency to invade terminal hepatic venules (18).. The definitive diagnosis of this malignant vascular tumor requires immunohistochemical evidence of endothelial differentiation. Identification of dendritic and/or epithelioid cells positive for endothelial cell markers will confirm the diagnosis. Immunohistochemical reactivity for FVIII-RAg ( von Willebrand's factor), CD31 and CD34 have been demonstrated in endothelial cells (16,17). The presence of immunohistochemical reactivity for FVIII-RAg ,CD31 and CD34 demonstrated the epithelioid endothelial cells and absolute diagnosis of HEH in our case. Increasing the index of suspicion and familarity with the radiological and histological characteristics of HEH facilitate accurate diagnosis.

HEH occurs mainly in adults, with a higher prevalence in women. Association with oral contraceptives and a possible hormonal influence on the development of HEH have been suggested (20), as has exposure to vinyl chloride, and a possible etiology from major trauma to the liver (10,14). No positive correlation between HEH and any form of hepatitis can be confirmed. We did not determine any of the possible etiologic factors in our patient and none of the etiopathogenic factors which have so far been described for this tumor were definite.

Different therapeutic approaches are suggested in HEH: partial hepatectomy, orthotopic liver transplantation and chemotherapy with different agents such as adriamycin and interferon (4,8,9,15,21-23). Because the clinical course of the disease reported in the literature is quite variable, it is impossible to assess their respective effectiveness because of the natural history of HEH. Glisson's capsule infiltration, nuclear atypia and proliferation index have not seen shown to be predictors of the behavior of the tumor, although high cellularity is reported to be correlated with poor clinical outcome (15). In the literature, the primary treatment of choice is radical hepatic resection (4,8,9,15). No attempt at local resection should be attempted if multifocal HEH of multicentric origin occurs. In this case orthotopic liver transplantation may be a curative procedure. The role of adjuvant chemotherapy and radiotherapy remains unclear. Surgical resection or liver transplantation is the recommended treatment in the largest series and reviews (9,15). In our case we treated the patient with orthotopic liver transplantation and follow up did not include without adjuvant treatment.

In conclusion, HEH is a rare tumor. Accurate differential diagnosis between HEH and other primary and secondary liver tumors should be obtained by means of radiologic and immunohistologic studies. Laparotomy and sometimes open biopsy may be needed to establish the correct diagnosis. Surgical resection or liver transplantation is recommended following definitive diagnosis of the disease.

## REFERENCES


1. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for carcinoma. Cancer 1982;50:970-81.
2. Weiss SW, Ishak KG, Dail DH, et al. Epithelioid hemangioendothelioma and related lesions. Semin Diagn Pathol 1986; 3: 259-87.
3. Ellis GL, Kratochvil III FJ. Epithelioid hemangioendothelioma of the head and neck: a clinicopathologic study of twelve cases. Oral Surg Oral Med Oral Pathol 1986;61:61-8.
4. Ishak KG, Sesterhenn IA, Goodman ZD, et al. Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. Hum Pathol 1984;15:839-52.
5. Uchimura K, Nakamuta M, Osoegawa M, et al. Hepatic epithelioid hemangioendothelioma. J Clin Gast 2001; 32: 431-4.
6. Clements D, Hubscher S, West R, et al. Epithelioid hemangioendothelioma: a case report. J Hepatol 1986;2:441-9.
7. Kahawe T, Tagawa K, Unuma T, et al. Hepatic epithelioid hemangioendothelioma in a young female. Dig Diş Sci 1987; 32: 1422-7.
8. Bancel B, Patricot LM, Coillon P, et al. Hepatic epithelioid hemangioendothelioma. A case with liver transplantation. Review of the literature. Ann Pathol 1993; 13(l):23-8.
9. Lauffer JM, Zimmermann A, Krabenbuhl L, et al. Epithelioid hemangioendothelioma of the liver. Cancer 1996;78:2318-27.
10. Banerjee B, Rennison A. Epithelioid haemangioendothelioma of liver: a vascular tumor easily mistaken for metastatic carcinoma on ultrasound imaging. Br J Radiol 1992; 65: 611-3.
11. Walsh MM, Hytiroglu P, Thung SN, et al. Epithelioid hemangioendothelioma of the liver mimicking Budd-Chiari syndrome. Arch Pathol Lab Med 1998;122:846-8.
12. Furui S, Itai Y, Ohtomo K, et al. Hepatic epithelioid hemangioendothelioma: report of five cases. Radiology 1989; 171:63-8.
13. Van Beers B, Roche A, Mathiue D, et al. Epithelioid hemangioendothelioma of the liver: MR and CT findings. J Comput Assist Tomogr 1992;16:420-4.
14. Shin MS, Carpenter JT, Ho KJ. Epithelioid hemangioendothelioma: CT manifestations and possible linkage to vinyl chloride exposure. J Comput Assist Tomogr 1991; 15: 505-7.
15. Makhlouf H, Ishak K, Goodman Z. Epithelioid hemangioendothelioma of the liver. Cancer 1999;85:562-82.
16. Ramani P, Bradley NJ, Fletcher CD. QBEND/10, a new monoclonal antibody to endothelium: assessment of its diagnostic utility in paraffin sections. Histopathology 1990;17:237-42.
17. Tsuneyoshi M, Dorfman HD, Bauer TW. Epitheliod hemangioendothelioma of bone: a clinicopathologic, ultrastructural, and immunohistochemical study. Am J Surg Pathol 1986;10:754-64.
18. Eckstein RP, Ravich RBM. Epithelioid hemangioendothelioma of the liver: report of two cases histologically mimicking veno-occlusive disease. Pathology 1986;18:459-62.
19. Gambacorta M, Bonacina E. Epithelioid hemangioendothe-

lioma: report of a case diagnosed by fine-neddle aspiration. Diagn Cytopathol 1989;5:207-10.

20. Dean PJ, Haggitt RC, O'Hara CJ. Malignant epithelioid hemangioendothelioma of the liver in young women: relationship to oral contraceptive use. Am J Surg Pathol 1985; 10: 695-704.
21. Idılman R, Dokmeci A, Beyler AR, et al. Successful medical treatment of an epithelioid hemangioendothelioma of the liver. Oncology 1997; 54:171-5.
22. Roudier-Pujol C, Enjolras O, Lacronique J, et al. Multifocal epithelioid hemangioendothelioma with partial remission after interferon alfa-2a treatment. Ann Dermatol Venereol 1994;121:898-904.
23. Aizawa Y, Watanabe F, Fujise K, et al. A case of epithelioid hemangioendothelioma of the liver diagnosed by liver biopsy under laparoscopy and treated with interleukin 2 (IL2). Nippon Shokakibyo Gakkai Zasshi 1991;88:2904-9.