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Interferon Alpha-2B and Liver Resection to Treat Multifocal Hepatic Epithelioid Hemangioendothelioma: A Relevant Approach to Avoid Liver Transplantation

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ABSTRACT:

Background. Hepatic epithelioid hemangioendothelioma is a rare malignant tumor of vascular origin with frequent multifocal appearance. Liver resection may cause tumor spread. Liver transplantation has been indicated for unresectable nodules. We hypothesized that adjuvant interferon treatment is effective to prevent metastasis after liver resection. We report a case of multifocal hepatic epithelioid hemangioendothelioma successfully treated with interferon pulse therapy and bilobar hepatic resection.

Methodology. CT scan and magnetic resonance imaging diagnosed three nodules in the liver (segments IV, VI and VII). Histopathology and specific immunostaining of a percutaneous nodule biopsy confirmed the diagnosis of hepatic epithelioid hemangioendothelioma. The treatment protocol included daily interferon alpha 2b 9 weeks before and 1 week after resection of liver segments IV, VI and VII.

Results. The postoperative outcome was complicated by a self-limited biliary fistula. The patient remains tumor free at 3 years after liver resection and currently enjoys excellent health.

Conclusion. Interferon pulse therapy and hepatic resection was a good option to treat multifocal bilobar hepatic epithelioid hemangioendothelioma; it may prevent metastasis dissemination.

HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA (HEH) is a rare tumor of endothelial origin, characterized by an epithelioid appearance and vascular endothelial histogenesis.[1–3] The diagnosis of HEH is frequently complex. Several cases have been misdiagnosed as sclerosing cholangiocarcinoma, metastatic carcinoma, fibrolamellar hepatocellular carcinoma, sarcoma, and mixed tumors, among others.[1–3]

HEH is generally unresponsive to radiotherapy or chemotherapy. Hepatic involvement tends to be multifocal and bilobar. Different from other liver tumors, HEH does not seem to arise a background of chronic liver disease or hepatitis. This peculiarity permits wide hepatic resection to treat this tumor.[1–3]

Tumor resection is the definitive treatment for HEH. The extension of resection has been a matter of controversy. It depends on the size and location of the lesions. Whenever possible, hepatic resection is the treatment of choice; however, tumor spread after this procedure is a real, uncontrolled possibility.[4–6] Segmental hepatic resection techniques have expanded the possibilities to treat multifocal and bilobar hepatic tumors without requiring liver transplantation.[4–7]

Liver transplantation has been recommended for unresectable tumors. Some authors prefer liver transplantation because it avoids metastasis related to liver resection and assures that the entire tumor will be removed.[8–11] On the other hand, some series have reported high mortality rates associated with liver transplantation to treat this tumor.

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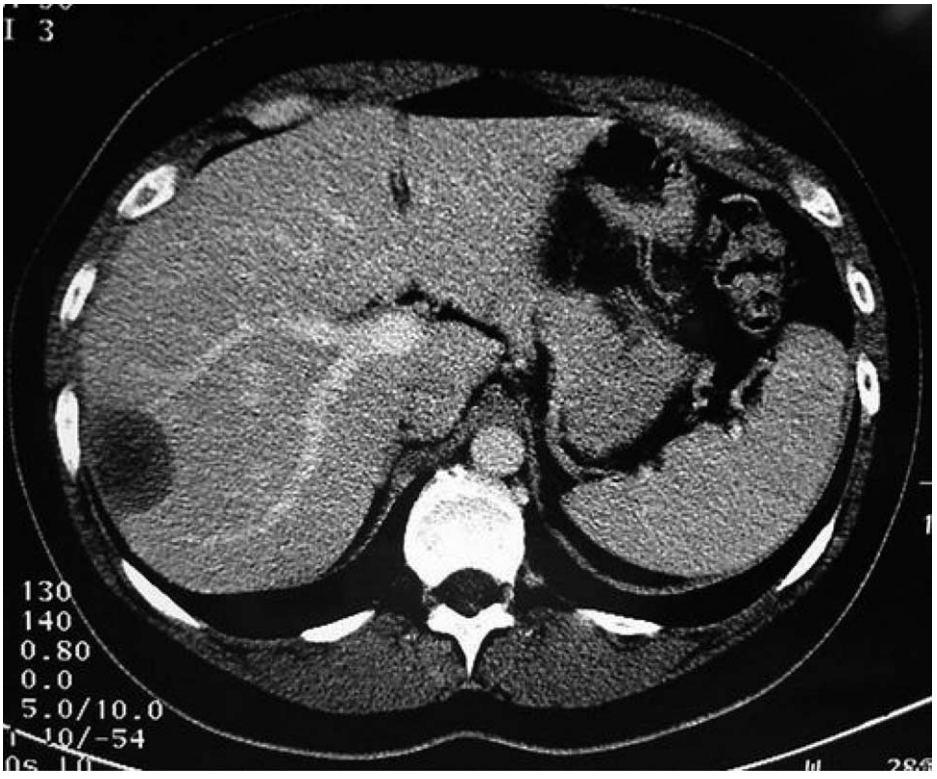

Fig 1. Abdominal computed tomography shows a nodule in the segment VII of the liver.

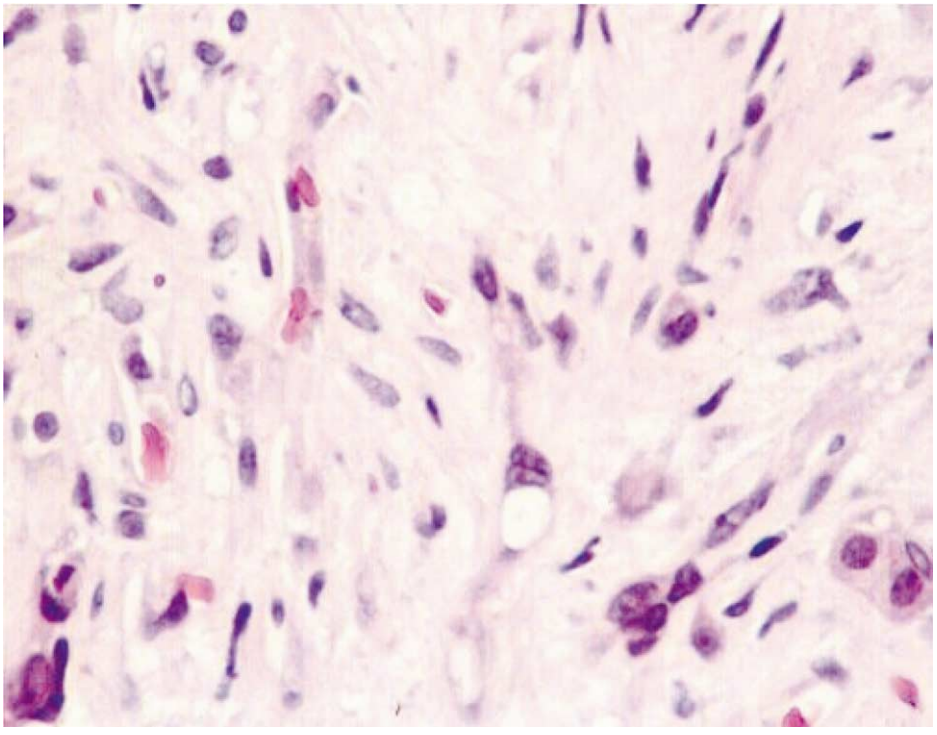

Fig 2. Abundant myxohialine stroma and red cells in abortive vascular lumens (HE, 400X).

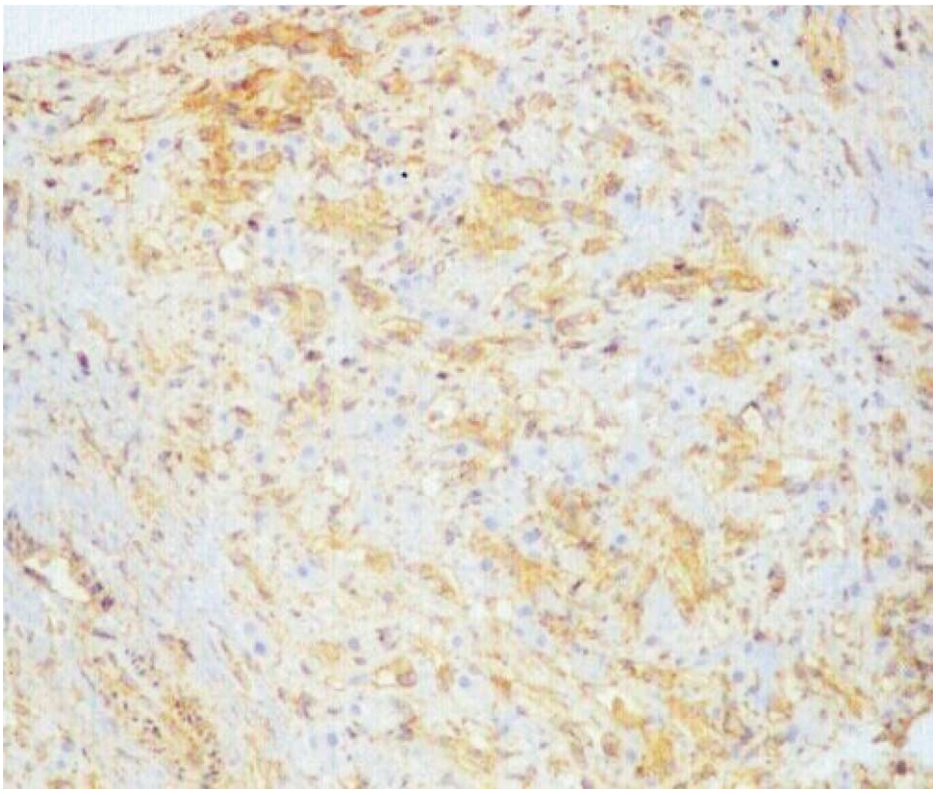

Fig 3. Intense positively to vimentin in tumor cells (200X).

The pleiotropic cytokine INF-alpha 2-b has produced beneficial effects in the treatment of a diverse array of malignant tumors.[12] There are only two reports in the literature describing the use of interferon alpha 2b as a coadjuvant treatment for HEH. IFN therapy was used to treat HEH metastasis after liver transplantation. Despite tumor size reduction, the patient developed graft rejection and died due to transplant-associated complications.[8] The other patient received IFN therapy 8 months before liver transplantation and achieved good evolution at 42 months after surgery.[1]

Interferon therapy has not been reported to be combined with liver resection to treat HEH. We hypothesize that IFN therapy and hepatic multifocal resection would be a relevant approach to prevent metastatic dissemination and treat bilobar HEH. The aim of this report was to describe the first case of HEH successfully treated by interferon alpha-2b combined with multifocal hepatic resection.

CASE REPORT

A 38-year-old Caucasian female was admitted with upper abdominal discomfort. She was otherwise healthy without relevant past medical or surgical history. She denied exposure to blood transfusions, oral contraceptives, vinyl chloride, thorotrast, or industrial toxins. She did not smoke or drink alcohol. Physical examination was unremarkable. All laboratory results were within normal limits. No positive markers for hepatitis A, B, or C were recorded. Serum tumor markers were also normal. Abdominal ultrasound examination revealed two tumors in segments VI and VII of the liver. Abdominal CT scan and MRI confirmed the presence of tumors and another nodule in segment IV. The size of the nodules in segments IV, VI, and VII (Fig 1) were 9, 14 and 35 mm, respectively. An ultrasound guided needle biopsy was performed in the nodule of segment VII. Microscopic analysis disclosed epithelioid, dendritic, and intermediate cells in varying degrees of cellularity, intracytoplasmic vacuolations, and occasionally erythrocytes from primitive vessels. The cells were embedded in a stroma that varied from myxoid or chondromatoid to densely fibrotic. Immunohistochemistry staining showed groups of tumor cells presenting abundant myxohyaline stroma with red cells seen in abortive vascular lumens (Fig 2). The tumor cells showed intensely positive immunostaining for vimentin (Fig 3); factor VII-related antigen; lectin *UEA*; and cytoplasmic and membranous CD31 lymphocyte subsets (Fig 4), confirming the diagnosis of HEH. The treatment followed a protocol of daily subcutaneous doses of interferon alpha-2b (three million units) 9 weeks before and 1 week after liver resection of segments VI and VII and subsegmentectomy of IVb with clear surgical margins. Blood transfusion was not necessary, the patient was discharged from the hospital on postoperative day 4. The early postoperative period was complicated by a selflimited biliary fistula. The patient remains tumor free at 3 years after liver resection and enjoys excellent health.

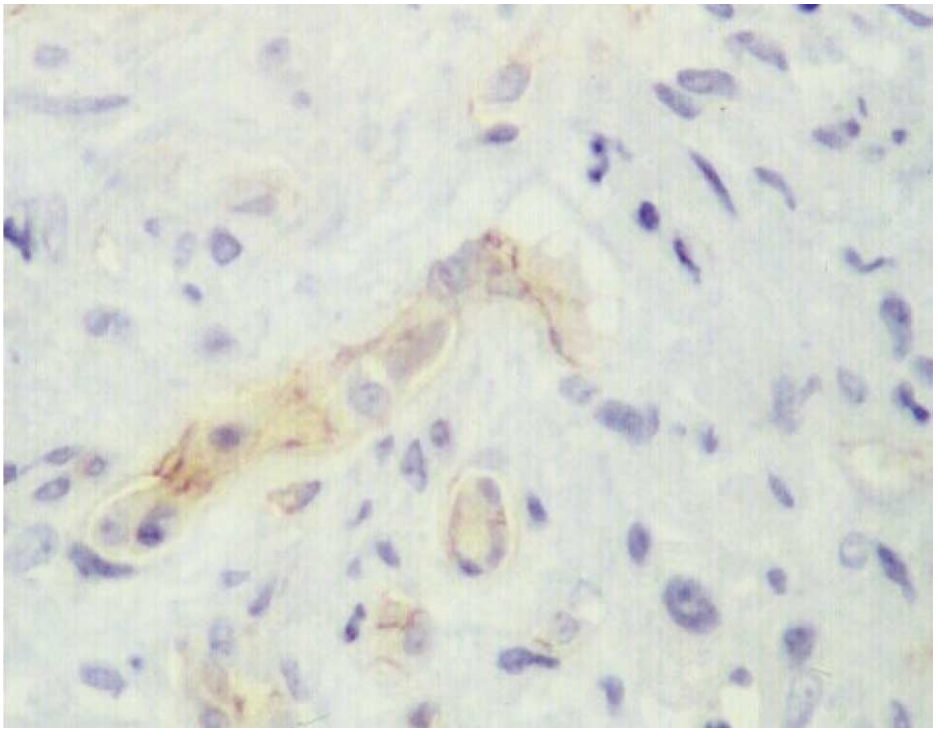

Fig 4. Positively to CD31 in tumor cells (400X).

DISCUSSION

HEH has variable malignant potential, ranging between benign hemangioma and malignant angiosarcoma.[1–3] Its etiology is unknown, but associations with oral contraceptives, vinyl chloride injection, or trauma have been reported.[1–3] HEH has an overall survival rate of 43% in 5 years.[1] Metastasis has been documented in 27% of cases, mainly in the lungs and abdominal lymph nodes.

Symptoms of HEH are nonspecific: abdominal pain; weight loss; and not often, jaundice. The tumor is often encountered as an incidental radiological finding.[1–3] Differential diagnosis of HEH may be difficult due to its varied radiological pattern and the pleomorphism of the tumor cells.[1–3,12,13]

The radiological appearance of HEH may show a nodular pattern of liver infiltration, a dense fibrosis, hypovascular central area, and a peripheral hyperemic rim.[1–3,12–14] It creates a fibrotic reaction in the surrounding liver parenchyma, which results in capsular retraction, a feature that is strongly suggestive of hepatic epithelioid hemangioendothelioma.[1–3,12–14]

No reliable parameters have been identified to predict the biologic behavior of HEH; its clinical course appears to be extremely variable.[1–3,12,13] Early diagnosis is fundamental for the correct management and treatment of HEH,[13,14] unfortunately, this situation is unusual. The reasons for late diagnosis include indolent and nonsymptomatic course of the disease, lack of serum tumor marker, and requirement of tumor biopsy and immunostaining for specific markers (vimentin, factor VIII-related antigen [FVIII-RAg], CD31, and CD34) to confirm the diagnosis.[1,11,13,14] The presence of vimentin, FVIII-RAg, CD31, and CD34 in a biopsy sample indicates endothelial proliferation in the tissue, confirming the diagnosis of HEH.

The indication for resection versus transplantation to treat HEH is a topic of debate and, considering the rarity of this tumor, the controversies between these two procedures will be difficult to settle in a scientific manner. Liver resection may be curative. Unfortunately, the diagnosis of HEH is often delayed, when extensive involvement of the liver is a common finding.[1–4,13] In these instances, radical resection may cause fulminant hepatic failure, and conservative hepatectomy may not remove the tumor completely with subsequent local or distant metastasis.[5]

Improvements in the understanding of the intrahepatic anatomy have increased the indications for segmental liver resections. Segment-oriented resection allows maximal conservation of normal liver parenchyma.[5–7] This approach has a great potential to be used for HEH because this disease course, without underlying liver disease, permits complex liver resections.

For advanced HEH, liver transplantation has been proposed.[5,8–11] The results in two small series from Pittsburgh showed 5-year survivals of 76% and 71.3%.[10,11] However, data on 88 patients transplanted between 1987 and 2001 from US Scientific Registry of Transplant Recipients showed less favorable outcomes. In these patients, the survival rates after 1 and 5 years were 61.2% and 44.2%, respectively.[8]

In a large series of HEH, six patients where successfully treated with resection, while two of seven patients treated with liver transplant died within 4 and 5 years.

On the other hand, Ben-Haim et al observed that two patients treated with local resection experienced early aggressive recurrences and death. These authors speculated that after liver resection the hepatotrophic signaling during regeneration may stimulate HEH proliferation, converting the residual indolent disease into an aggressive malignancy.[4]

Interferon therapy for HEH has been proposed for tumor reduction and metastasis prevention.[8] Kayler et al used interferon for treatment of metastatic HEH after liver transplantation, observing palliation of symptoms and reduction of the lesions.[8] Unfortunately, the treatment had to be discontinued due to graft rejection and tacrolimus-induced thrombocytopenic purpura, renal failure, and bacterial pneumonia, leading to patient death at 15 months after transplantation. These authors speculated that the most beneficial time for interferon therapy should be before transplantation.

After an exhaustive multidisciplinary discussion, we decided to use adjuvant interferon therapy in the present treatment protocol. The rationale for the use of interferon before surgery was to promote tumor reduction and to prevent metastasis, mainly during hepatic manipulation for resection. After surgery, interferon was used to avoid HEH proliferation due to hepatotrophic signaling during regeneration.

It is noticeable that disease-free survival after 3 years postresection is not sufficient to implicate interferon adjuvant therapy as the reason for cure. However, the use of this approach holds theoretical merit, probably having a good impact on prevention of metastasis associated with liver manipulation during the surgery. Therefore, for the treatment of multifocal HEH, a pulse of interferon associated with liver bilobar segmentectomies is a alternative to prevent metastasis and avoid radical liver resection or liver transplantation.

In conclusion, a pulse of interferon therapy and bilobar segmentectomy is a useful option for selected cases of multifocal HEH thereby avoiding the indication for liver transplantation.

REFERENCES

1. Makhlouf H, Ishak KG, Goodman ZD: Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer 3:562, 1999

2. Ishak KG, Sesterhenn IA, Goodman MZD, et al: Epithelioihemangioendothelioma of the liver: a clinicopathologic and follow-up study 32 cases. Hum Pathol 15:839, 1984

3. Lauffer JM, Zimmerman A, Triller J, et al: Epithelioid hemangioendothelioma of the liver: a rare hepatic tumor. Cancer 78:2318, 1996

4. Imanishi H, Kawata M, Yanagihara M, et al: Epithelioid hemangioendothelioma of the liver associated with thrombocytopenia and coagulopathy. Hepatogastroenterology 49:>1673, 2002

5. Ben-Haim M, Roayaie S, Ye MQ: Hepatic epithelioid hemangioendothelioma: resection or transplantation, which and when? Liver Transpl Surg 5:526, 1999

6. Kemeny MM: Hepatic resection: when, what kind, and for which patients. J Surg Oncol 2(Suppl):54, 1991

7. Tannenbaum CS, Tubbs R, Armstrong D, et al: The CXC chemokines IP-10 and Mig are necessary for IL-12-mediated regression of the mouse RENCA tumor. J Immunol 161:927, 1998

8. Kayler LK, Merion RM, Arenas JD, et al: Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. Transplantation 74:128, 2002

9. D'Annibale M, Piovanello P, Carlini P, et al: Epithelioid hemangioendothelioma of the liver: case report and review of the literature. Transplant Proc 34:1248, 2002

10. Marino I, Todo S, Tzakis A: Treatment of hepatic hemangioendothelioma with liver transplantation. Cancer 62:2079, 1988

11. Madariaga J, Marino I, Karavias I: Long-term results after liver transplantation for primary hepatic epithelioid hemangioendothelioma. Ann Surg Oncol 2: 483, 1995

12. Machado MA, Herman P, Machado MC: Standardized technique for segmental right liver resections. Arch Surg 2003 (in press)

13. Miller WJ, Dodd GD, Federle MP, et al: Epithelioid hemangioendothelioma of the liver: imaging findings with pathologic correlation. Am J Radiol 159:53, 1992

14. Demetris AJ, Minervini M, Raikow RB, et al: Hepatic epithelioid hemangioendothelioma: biological questions based on pattern of recurrence in an allograft and tumor immunophenotype. Am J Surg Pathol 21: 263, 1997