

# Epithelioid Hemangioendothelioma of the Liver: Etiology, Natural History and Treatment

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Received January 6, 2008; accepted May 18, 2008.

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**KEY WORDS:** epithelioid hemangioendothelioma, liver neoplasms, therapy.

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## Introduction

Epithelioid hemangioendothelioma (EHE) is an uncommon vascular tumor, which also has been called histiocytoid haemangioma. This low-grade malignant tumor was first described as a distinctive entity in 1982 by Weiss and Enzinger<sup>[1]</sup>. Histopathologically, EHE is characterized by round or spindle-shaped endothelial cells with cytoplasmic vacuolation<sup>[2]</sup>. The tumor may occur in numerous organs, including liver, lung, parotid gland, skin, pleura, thyroid, spleen, cardiac valve, radial artery, oral cavity and parapharyngeal space<sup>[2-11]</sup>. Many cases have been reported, but its etiology and natural history remain unclear.

After obtaining informed consent, the authors report our case of primary liver EHE along with a review of the literature, emphasizing the natural history, our choice treatment and the etiologic factors, especially the possible relationship to long-term use of oral contraceptives.

## Case Report

A 45-year-old female patient presented with a 18-month history of upper abdominal pain associated with abdominal distension and nausea. The pain was mild, constant, dull, and increased with a change in posture or sudden movement. She also displayed fatigue and a weight loss of 6 kg over the preceding 5 months. She had been unwilling to undergo a liver biopsy or laparotomy over the past 18-months. The patient had no history of fever, jaundice, gastrointestinal bleeding or edema of her feet. She had taken oral contraceptives for 16-years following her second daughter's birth until she began to feel upper abdominal pain 18-months ago. She had no history of trauma, therapeutic radiation, hormone therapy, hepatitis, and blood transfusion, use of cigarettes or alcohol. There was no history of exposure to vinyl chloride, thorotrast or any other industrial toxin. Her family had a negative history for malignant disease.

On examination, the patient was pale, but not icteric. Systemic examination of the central nervous system, cardiovascular system, and respiratory system was unremarkable. She had mild tenderness in the right upper quadrant of the abdomen without hepatosplenomegaly. Laboratory results were normal, including liver function tests, viral markers for hepatitis B and C viruses, serum  $\alpha$ -fetoprotein and carcinoembryonic antigen levels. Ultrasonography of the abdomen was conducted 4 times during one and a half years, revealing an occupying lesion in the Couinaud segment V. The lesion measured 3.1 cm  $\times$  3.1 cm in March 2005, 3.7 cm  $\times$  3.5 cm in September 2005, 4.3 cm

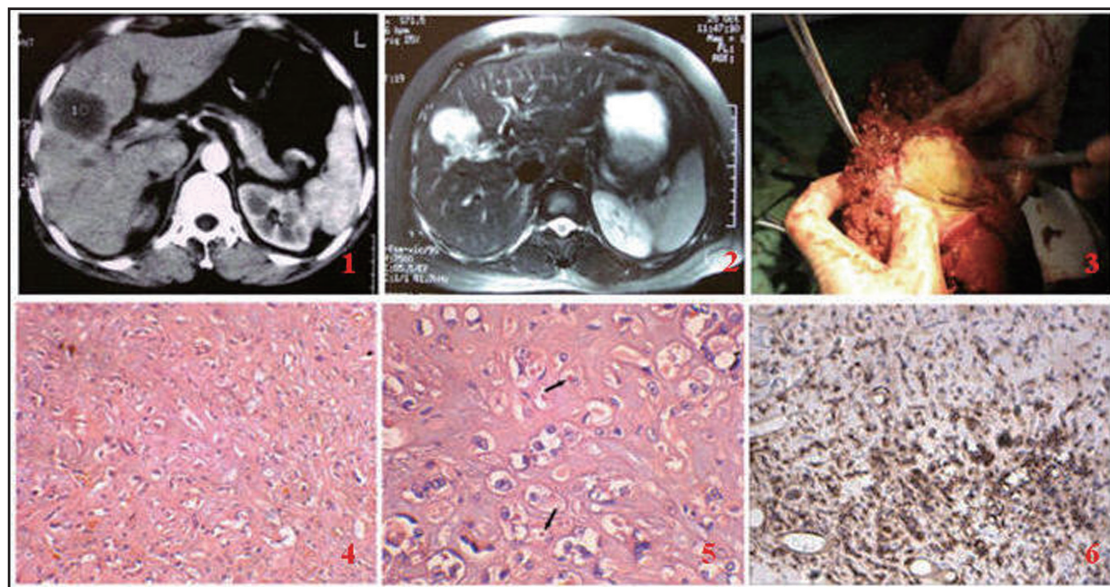


Fig.1. Spiral CT examination of the liver performed after administration of intravenous contrast medium (arterial phase) shows several hypodense lesions with a non-obviously peripheral enhanced rim.

Fig.2. Magnetic resonance imaging. A high-density zone of necrosis is observed in the centre of the lesion.

Fig.3. A slice of excised lesion and healthy liver tissue showing all of the tumor nodules.

Fig.4. The tumor is composed of short cords and small nests of epithelioid tumor cells in a desmoplastic stroma (H&E stain,  $\times 200$ ).

Fig.5. Presence of a neoplastic cell group in the lesion of the liver. Notice the intra-cytoplasmic vacuole of this tumor cell containing erythrocytes (arrow; H&E stain,  $\times 400$ ).

Fig.6. Immunostaining for CD34 shows diffuse and intense staining of tumor cells (S-P stain,  $\times 100$ ).

$\times 3.9$  cm in April 2006, and  $5.4$  cm  $\times 4.6$  cm in September 2006. Computed tomography (CT) of the abdomen confirmed twice the ultrasound finding:  $3.8$  cm  $\times 3.6$  cm in September 2005, and  $5.5$  cm  $\times 4.6$  cm in September 2006 (Fig.1). Magnetic resonance imaging (MRI) of the abdomen which was performed in September 2006 (Fig.2), also revealed focal hepatic lesions in segments V, of a  $5.5$  cm  $\times 4.6$  cm size, suggesting a malignant disease.

Based on these findings, the patient was subjected to an exploratory laparotomy in October 2006. In a sub-costal laparotomy, 3 nodules were detected in the liver: a  $5.5$  cm  $\times 4.5$  cm nodule in segment V, a  $0.4$  cm  $\times 0.3$  cm in segment IV, and a  $0.4$  cm  $\times 0.4$  cm nodule in segment VI. No other pathological signs were detected in the remaining liver and abdominal cavity. Liver segment IV, V, VI were excised with a margin of healthy tissue (Fig.3). Blood transfusions were not necessary. The patient's postoperative course was uneventful.

In an anatomopathological study, a well-defined neoplastic growth was observed (Figs.4 &5), comprised of cords, rows of cells, and loose cells in a sclerotic stroma. The cells were round or spindle-shaped endothelial in appearance, and showed many intra-cytoplasmic vacuoles. Some cords formed vacuoles containing red blood cells (Fig.5). Immunohistochemical stains were positive for CD34 (Fig.6), factor VIII-related antigen and vimentin, but negative for CK, AFP antigen, AAT, SMA, MC and S-100.

At the last follow-up visit one year after the surgery, the patient was well and had no signs of recurrence.

## Discussion

EHE of the liver is a rare multifocal vascular tumor with a female preponderance that can develop at any age<sup>[12]</sup>. It has variable malignant potential, ranging between benign hemangioma and malignant angiosarcoma. Its true incidence is unknown, because the diagnosis of EHE is frequently complex, and many such tumors have been misdiagnosed as metastatic carcinoma, cholangiocarcinoma, hepatocellular sclerosing carcinoma, or angiosarcoma<sup>[1,13]</sup>.

The etiology of this tumor remains unclear, because of its rare incidence and complex pathogenesis. An association with oral contraceptives has been reported, and some cases have been related to exposure to vinyl chloride<sup>[14,15]</sup>. Other possible etiologic factors have been suggested, such as hepatitis C<sup>[16]</sup>, chronic liver disease, alcohol abuse, sclerosing cholangitis<sup>[17]</sup>, major trauma to the liver, hormonal treatment, and occupational contaminants<sup>[12]</sup>. In our reported case, long-term oral contraceptive usage may be the etiologic factor. The patient had taken birth control pills for 16 years prior to discovery of her tumor. We tried to search for other possible pathologic causes but failed to find a significant relationship. She had no history of hepatitis, blood transfusion, smoking, alcohol intake, or contact with an industrial toxin. This may suggest a close relationship between liver EHE and long-term use of oral contraceptives. But this association cannot explain the occurrence of EHE in males and children, so there must be other etiologic factors.

The clinical course and behavior of EHE is highly unpredictable. Most patients have non-specific symptoms and in many patients the tumor is diagnosed serendipitously. The common symptoms are upper abdominal pain, anorexia, and weight loss. The most common sign is hepatosplenomegaly. The most evident finding in EHE is raised alkaline phosphatase levels, which occurs in approximately 70% of the patients<sup>[16,18]</sup>. Our patient showed typical symptoms, but no sign or significant biochemical alterations were detected. Imaging (ultrasonography, CT, MRI) of the liver provided the most valuable finding because our patient refused a liver biopsy. Significantly, the liver nodule of the EHE increased during a 18-month period, from 3.1 cm × 3.1 cm in March 2005 to 5.4 cm × 4.6 cm in September 2006. This finding gives us at least two points of significant information. First, that the speed of liver EHE growth is slow, and that the natural developmental history is longer compared to other malignant hepatocellular tumors. Second, that EHE of the liver may have a lower malignant potential than other liver malignant tumors.

There are few treatment options. Chemotherapy and radiotherapy yield no improvement in survival. Surgical resection or orthotopic liver transplantation are recommended treatments for liver EHE<sup>[12,18]</sup>. Two forms of the neoplasm have been described: a nodular form and a diffuse form. In most patients (66%), there are multiple nodular lesions, distributed throughout the hepatic parenchyma<sup>[19]</sup>. From the literature, the primary treatment of choice is radical hepatic resection<sup>[12]</sup>. The extension of resection depends on the size and location of the lesions. But, for EHE with a multinodular diffuse form, the choice of treatment when a radical resection cannot be undertaken should be an orthotopic liver transplant. Administration of interferon and bi-lobe segmentectomy may be a useful option for selected cases of multifocal EHE, thereby avoiding the need for liver transplantation<sup>[20]</sup>. Our patient had 3 nodules in her liver comprised of a diffuse form. Fortunately, the 3 nodules were located in the right lobe and a radical hepatic resection of segments IV, V, VI was performed successfully.

The prognosis of liver EHE is better than that of other hepatic neoplasms, although there are descriptions of cases showing aggressive progression. Therefore, treatment should not be conservative, and patients should be appropriately selected for radical hepatic resection or orthotopic liver transplantation. Through the present case report, we suggest there is a close relationship between liver EHE and long-term use of oral contraceptives. In addition, our case suggests that EHE of the liver has lower malignant potentials, slow growth and has a longer natural history compared to other hepatic neoplasms.

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