Epitheloid Hemangioendothelioma in Patient with Liver Transplantation

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ABSTRACT

Malignant hepatic epithelioid hemangioendothelioma (HEH) is a rare malignant tumor of vascular origin with unknown aetiology and a variable natural course. At the time of diagnosis, most patients present with multifocal tumours lesions that involve both liver lobes. From the therapeutic aspect, liver resection (LRx), liver transplantation (LTx), chemotherapy, radiotherapy, and/or immunotherapy have been used in the treatment of patients with HEH. However, because of the rarity of this tumor and its unpredictable natural history, it is impossible to assess the effectiveness of these respective therapies. In this report, our objective was to present clinical aspects, diagnostic options, therapeutic modalities, and the clinical outcome of single patient with LTx because of this rare tumor.

Key words: hepatic epithelioid hemangioendothelioma, liver transplantation, fine needle aspiration cytology

Introduction

Malignant hepatic epithelioid hemangioendothelioma (HEH) is a rare malignant tumor of vascular origin with unknown aetiology and a variable natural course. The term epithelioid hemangioendothelioma was defined as a distinct entity first by Weiss and Enzinger in 1982 as a soft tissue vascular tumor of endothelial origin with a clinical course between benign haemangioma and angiosarcoma1. HEH most commonly affects adult females. At the time of diagnosis, most patients present with multifocal tumours lesions that involve both liver lobes. Most common sites of extra hepatic involvement are lungs, peritoneum, lymph nodes, and bones1.

Based on current knowledge, no definitive etiology has been confirmed as a causative factor for HEH. Some possible risk factors of HEH include oral contraceptives, vinyl chloride, asbestos, major trauma to the liver, viral hepatitis, primary biliary cirrhosis, gold compounds and alcohol consumption2. HEH, in contrast to many other types of primary liver tumor, does not typically arise in a background of chronic liver disease, as described previously2.

Clinical manifestations of HEH are uncommon and non-specific. Makhlouf et al. reported findings in a series of 137 patients with this tumor3. At the time of diagnosis, 25% of reported patients were asymptomatic. Among symptomatic patients, the most common clinical manifestations were right upper quadrant pain (48.6%), hepatomegaly (20.4%), and weight loss (15.6%). Weakness, anorexia, epigastric mass, ascites, nausea/emesis, jaundice, and fatigue were the next most common presenting manifestations. Eighty-seven percent of patients presented with a multifocal tumor that involved both liver lobes, whereas only 13% of the patients had a unifocal tumor. The right lobe was affected more than the left lobe in both multifocal and unifocal presentations. Extra hepatic involvement at the time of diagnosis was observed only in 36.6% of patients. Out of other reported sites spleen is involved in 3.2% of cases. Eighty percent of pa-

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patients had abnormal laboratory findings. Most tumor markers (e.g., alpha-fetoprotein, carcinoembryonic antigen, and CA 19-9) were in the normal range and, in the current context, were suitable only for ruling out other primary or metastatic liver tumors.

On ultrasonography, most frequently (66%), the lesions are hypoechoic relative to the adjacent hepatic parenchyma. Other patterns of echogenicity include heterogeneous (22.5%), hyperechoic (6.2%), and isoechoic with hypoechoic rim (5%) appearance. On computed tomography (CT) scans most often low-density abnormal pattern is reported (98% of patients). Normal CT scans are reported in 1.4% of patients. HEH usually is hypointense on T1-weighted images and hyperintense on T2-weighted images by magnetic resonance images. The target appearance of the lesions may be caused by the presence of a central sclerotic zone and a peripheral region of cellular proliferation. Central low-signal areas may correspond to haemorrhage, coagulation necrosis, and calcification; whereas peripheral high signal intensity corresponds to oedematous connective tissue and viable tumor. Angiographic examination of the liver is performed only in selected patients and reveals only moderate vascularization. In literature review findings were completely heterogeneous, ranging from hypo- to hyperperfusion.

Generally, in the nodular form, a specific diagnosis is impossible without performing a fine needle aspiration cytology or biopsy because the radiology findings are similar to those in some hepatic metastases. Tumor is characterized by an epithelioid or histioid morphology and a growth pattern with evidence of endothelial histogenesis. Cells show prominent mucin negative cytoplasmatic vacuoles. Red blood cells may be present within some of these vacuoles (reminiscent of primitive vascular channels). Its vascular nature is confirmed by positive staining for factor VIII-related antigen and/or other endothelial cell markers (CD31, CD34) in addition to the ultrastructural characteristics of well developed basal lamina, pinocytic vesicles, and, more specifically, Weibel-Palade bodies. Some cases show positivity to smooth muscle actin, vimentin and cytokeratin. Epithelial membrane antigen (EMA) and S-100 staining patterns are negative. Immunohistochemical identification of factor VIII related antigen is helpful in differentiating between metastatic carcinoma and primary epithelial liver tumors. Generally there is low mitotic activity and mild to moderate pleomorphism. Cases with tumor cells displaying cytological atypia, increased mitotic activity and necrosis and high cellularity could be related with worsen outcome. But clinical course of this tumor is quite variable and cytological analysis could not be used to predict disease outcome.

Clinical course of HEH is variable, ranging from a favourable disease with prolonged survival, even without therapy, to a rapidly progressive disease with a grave outcome. Liver resection therapy (LRx) is the treatment of choice in patients with resectable HEH. However, in patients with multifocal liver tumor the most common management procedure is liver transplantation (LTx). In addition, LTx is an acceptable option for patients who have HEH with extrahepatic manifestation. The 1-year and 5-year patient survival rates are 96% and 54.5%, respectively, after LTx; 39.3% and 4.5%, respectively, after no treatment, 73.3% and 30%, respectively, after chemotherapy or radiotherapy; and 100% and 75%, respectively, after (LRx).

Case Report

60 year old female patient with psoriatic arthritis was treated for six years with metotrexate (cumulative dose 460 mg) and gold compounds. Eight years before definite diagnosis patient presented with signs of liver damage (pathological aminotransferases) and multiple hypoechoic lesions on liver ultrasound. All psoriatic arthritis therapy thereafter was stopped. Laboratory oncogenic markers (AFP, CEA, CA 19-9, CA 152, CA 15-3) were all in normal ranges. By repeated biopsies malignant alteration was not confirmed and diagnosis of tumor lesions was undefined. For years ago patient developed signs of ascites. Biopics samples of tumor uninvolved liver tissue revealed cirrhosis. Because tests to all other etiological factors were negative (alcohol consumption, viral serology, immunological tests, and copper in biopic sample) etiology was related with postnecrotic changes. Since that time liver ultrasound and multislice CT displayed slow progression in size of confluent hypochoic/hypodense tumor lesions in both liver lobes (3 cm maximal diameter) and appearance of one new lesion (4 cm in diameter) in spleen. Some tumors displayed signs of central necrosis. Angiography revealed no signs of pathological arterial vascularization.

In our centre patient appeared one year ago with symptoms of upper quadrant pain, nausea, weight loss, weakness, ascites, and jaundice. Laboratory findings revealed elevated level of aminotransferases, alkaline phosphatase and gamaglutiltranspherase (within twice of upper normal level), hiperbilirubinemia (5 fold higher than upper normal limit), low protrombin time (64%), normocytic normochromic anemia (Hgb 90 MCV 34 (Figure 3), vimentin and factor VIII related antigen. Tumor cells were staining positive to anti CD31 (Figure 2), anti CD 34 (Figure 3), vimentin and factor VIII related antigen.

Multiple tumor lesions in cirrhotic liver were considered nonresectible. Since multiphocal malignant hemangioidothelioma is considered in literature for liver transplantation it was proposed to patient. According to rules of Eurotransplant organization patient was reconsidered as non standard exception in indication for liver transplantation.

Standard orthotropic liver transplantation with total spleenectomy was performed in December 2008. Expla-
Hepatic epitheloid hemangioendothelioma cells, fine needle aspiration cytology smears (May-Grunwald-Giemsa staining).

Fig. 1. Hepatic epitheloid hemangioendothelioma cells – positive immunostaining to CD31 (LSAB).

Fig. 2. Hepatic epitheloid hemangioendothelioma cells – positive immunostaining to CD34 (LSAB).

Discussion and Conclusion

HHE is rare vascular tumor of liver. Positive imaging findings in addition to certain features, such as occurrence in younger adults, the presence of numerous intrhepatic tumors with a good clinical condition, slow course of the disease, and the presence of intratumoral calcifications, are suggestive for HEH. But the definitive diagnosis of this rare liver tumor requires a cytological or histopathologic analysis. The diagnosis mostly is confirmed by immunohistochemical evidence of endothelial differentiation, as demonstrated by the presence of factor VIII-related antigen (in nearly all patients), the presence of CD34 (94%), and CD31 (86%). Often, a laparoscopic wedge or core biopsy is sufficient to encompass the architectural features of HEH, such as the intravascular characteristics. In presented case definite diagnosis was confirmed by fine needle aspiration cytology.

Variable patterns of the tumor may mimic other lesions. As in this case, in the literature review, approximately 60% to 80% of patients with HEH initially were misdiagnosed. The most common misdiagnoses are cholangiocarcinoma, angiosarcoma, hepatocellular carcinoma, metastatic carcinoma, and sclerosing hemangioma. Mixed hamartoma, spindle cell neoplasm, inflammatory pseudotumors, bile duct adenoma, cirrhosis, carcinoma with chondromyxoid change, venoocclusive disease, fibrolamellar carcinoma, postnecrotic fibrosis, and Budd-Chiari syndrome were less common misdiagnoses.
The management options for patients with HHE are numerous. Theoretically, LRx is the first choice for curative treatment of HEH. Like in this case, in majority of other patients, total resection is impossible because of the multicentricity of the lesions or anatomic difficulties: LTx is generally the most common treatment modality (44.8)8. Improved clinical outcomes after LTx in the last decade have provided further support in favour of undergoing LTx as curative treatment for HEH9. Significance of chemotherapy and/or radiotherapy is difficult to assess, mainly because of the lack of uniform treatment modalities and prospectively collected data.

According to earlier experience tumor can spread to other organs and presence of tumor cells displaying cytological atypia are not necessarily related with bad prognosis. In this regard, the unpredictable natural course and prognosis of HEH make it difficult to determine a correlation between morphologic grading or clinical staging and outcome. The life expectancy of patients with HEH potentially is good. Limited extrahepatic disease should not be considered an absolute contraindication to LTx10. Some authors have advocated LTx in the presence of extrahepatic involvement based on the reports of a 5-year survival rate between 48% and 71% in patients with HEH who had extrahepatic manifestations and underwent LTx2,11. Most recurrences occurred beyond 2 years after transplantation12.

This case report represents first case of successfully liver transplanted adult patient with multifocal HEH with extrahepatic spleen involvement in Croatia. In accordance with earlier experience, despite multifocal appearance of disease before LTx eight months after procedure there are no signs of disease recurrence. In patients with multifocal HHE and resectable extrahepatic disease LTx seems rational option.

REFERENCES


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EPITELOIDNI HEMAGIOTELIOM U BOLESNIKA S TRANSPLANTACIJOM JETRE

S A Ž E T A K

Maligni epiteloidni hemangioendoteliom jetre je rijetki maligni tumor porijeklom od stanica krvnih i/ili imunomodulatorne terapije. Obzirom na rijetkost navedenog tumora i nepredvidiv prirodni tijek bolesti nemoguće je generalno procijeniti efektivnost navedenih terapija. U ovom prikazu cilj je prikazati kliničke aspekte, dijagnostičke mogućnosti, terapijske modalitete i tijek bolesti kod bolesnica s transplantiranom jetrom uslijed navedenog rijetkog tumora.