

Characteristics and Treatment Strategy of Hepatic Angiomyolipoma: a Series of 94 Patients Collected from Four Institutions

Zhi-Gang Chang¹, Jin-Ming Zhang², Jiao-Qian Ying³, Yu-Ping Ge⁴

1) Department of General Surgery, Beijing Hospital; 2) Department of Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai; 3) Department of Emergency, China-Japan Friendship Hospital, East Yinghua Road, He Pingli, Chao Yang District, Beijing; 4) Department of Internal Medicine, Peking Union Medical College Hospital, Beijing, P.R. China.

Abstract

Aim. To report on a Chinese multicenter series of hepatic angiomyolipoma (HAML) patients and to study the characteristics and the treatment strategy of the disease. **Method.** Data of 94 patients diagnosed with HAML from four institutions of China between December 1997 and January 2008 were reviewed retrospectively. Immunohistochemical assays were performed on the surgical specimens and follow up studies were done in all the patients. **Results.** 52 of 94 patients (55.3%) showed no significant clinical symptoms. There were no specific findings on laboratory examinations. The correct preoperative diagnostic rate of ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) was 0% (0/94), 15.7% (11/70) and 22.7% (10/44), respectively. Regarding the treatment, 93 patients had a hepatectomy and 1 patient was treated by radiofrequency ablation. The postoperative pathology showed HAML in all the patients: 69 patients were studied with HMB-45 staining by immunohistochemistry and the positive rate was 100%. The postoperative follow-up rate was 91.5% (86/94), no sign of recurrence or metastasis was observed during the follow-up period. **Conclusion.** This is the largest HAML series reported in the literature. There are no specific signs and symptoms in HAML patients; the preoperative imaging diagnosis (including CT, MRI) is insensitive. The common pathological features include the basic histological components and expression of HMB-45. Conservative treatment is not suggested; surgical resection should be considered as a treatment choice for HAML.

Keywords

Hepatic angiomyolipoma – HMB-45 – diagnosis – surgical treatment.

Introduction

Hepatic angiomyolipoma (HAML) is a rare hepatic mesenchymal tumor, which usually has different distributions among adipose tissue, smooth muscle and blood vessels. Since its first description by Ishak et al in 1976 [1], more cases have been reported in the English literature with an increasing frequency in recent years [2-4] due to the development and popularity of diagnostic imaging techniques. However, all the studies of HAML are reported on the basis of small sample of case reports; up to now, the largest sample of cases reported in the English literature has been of 30 cases [5]. Due to the reduced number of patients, the clinical results and management of this disease is limited, thus large series of cases are required to summarize the clinical characteristics of HAML as well as its treatment strategies. At present, there is no obvious geographical difference in terms of the morbidity of HAML, and the etiology of HAML is still unclear. Although the combination of ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and angiography increases the accuracy in the diagnosis of HAML, the correct preoperative diagnostic rate of imaging studies has been reported to be less than 25% [6]. The preoperative confirmation is difficult due to lack of knowledge about its clinical and imaging features. In the past, this tumor was once considered an entirely benign and slow-growing lesion; some authors have suggested that this disease can be managed with conservative treatment [6]. However, since 2000, several reports have revealed that this kind of tumor can be malignant with evidence of recurrence [7, 8]. Therefore, the proper treatment of HAML has remained controversial.

We analyzed the characteristics and outcomes of a series of 94 HAML cases from China. Up to now, this is the largest series of case reports that have ever been published.

Material and methods

The clinical, imaging, pathological features, treatment and outcomes of 94 patients with HAML of four different Chinese large medical centers (Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University,

Received: 27.07.2010 Accepted: 03.11.2010

J Gastrointest Liver Dis

March 2011 Vol. 20 No 1, 65-69

Address for correspondence:

Zhi-Gang Chang, MD, PhD
Department of General Surgery
Beijing Hospital, 1st Dahua Rd.
Dongdan, Beijing 100730 P.R.China.
Email: zhigangchang@hotmail.com

Shanghai, and Beijing Hospital Ministry of Health, China-Japan Friendship Hospital, and Peking Union Medical College Hospital from Beijing) from December 1997 to January 2008 were analyzed retrospectively. The routine blood tests, liver function tests, hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), coagulation tests and serum tumor markers such as alpha-fetoprotein (AFP), cancer antigen 19-9 (CA19-9) and carcino-embryonic antigen (CEA) were studied in all patients. The values for AFP >15 ng/ml, CA19-9 > 37 U/ml and CEA > 5 ng/ml were considered positive. Hepatectomy was performed on 93 patients and percutaneous radiofrequency ablation was performed in 1 patient.

All surgical specimens were fixed in 10% formaldehyde, dehydrated routinely, and then paraffin embedded for routine hematoxylin and eosin (H&E) staining. All the diagnoses were pathologically confirmed by at least two pathologists independently. Immunohistochemical assays were performed using a three-step indirect peroxidase complex technique with the following antibodies: HMB-45 (DAKO, dilution 1:40), smooth muscle actin (SMA, DAKO, dilution 1:150), CD34 (DAKO, dilution 1:100), PCNA (Santa Cruse, dilution 1:100), cytokeratin 18 (CK18, Biogenix, dilution 1:80), and cytokeratin 19 (CK19, Biogenix, dilution 1:80). All patients were followed up.

Results

Patients and clinical findings

A total of 94 patients were diagnosed as having HAML, comprising 26 males and 68 females (1: 2.6). The median age was 42 years, ranging from 24 to 74 years. In our study, 42 (54.7%) patients were detected due to symptoms of abdominal discomfort, which included abdominal pain, abdominal fullness, palpable mass, etc; the other 52 patients (55.3 %) presented no symptoms and were identified incidentally by health check-ups or during medical examinations for other diseases. None of them had a history of renal angiomyolipoma (AML) or tuberous sclerosis. Nine patients had alcohol abuse, and 20 had smoking habits. The tumor location and size are shown in Table I.

Laboratory findings

Twelve patients (12/94, 12.8%) had a positive hepatitis B surface antigen (HBsAg), and four patients (4/94) had liver cirrhosis while one patient (1/94, 1.1%) was anti-HCV positive. According to the Child-Pugh classification, there were 84 (89.4%) patients in class A and 10 (10.6%) in class B. For all patients the blood, urine, and stool routine tests were within the normal range; the liver and kidney functions were normal; the CA19-9, CEA and AFP levels were all within the normal range.

Imaging findings

All the patients were examined by ultrasound; no one was diagnosed with HAML. Seventy patients underwent both plain CT and contrast-enhanced CT examination, only 11 of them were diagnosed as HAML (15.7%, 11/70) (Table

Table I. Patient's characteristics

Variable	Median (range)	n/total (%)
Sex		
Male		26/94 (27.7%)
Female		68/94 (72.3%)
Age (years)	42 (24-74)	
Alcohol abuse (≥100g daily)		9/94 (10%)
Smoking habits		20/94 (21.3%)
Symptoms		
No symptom		52/94 (55.3%)
Abdominal pain		25/94 (26.6%)
Abdominal fullness		8/94 (8.5%)
Other		9/94 (9.6%)
HAML diameter (cm)		
≤5		45/94 (47.9%)
5-10		40/94 (42.6%)
10-20		6/94 (6.4%)
≥20		5/94 (5.3%)
Tumor location		
Left lobe		29/94 (30.9%)
Right lobe		58/94 (61.7%)
Caudal lobe		8/94 (8.5%)
Left & right lobes		1/94 (1.1%)

II). The plain CT scan showed a well-defined, homogeneous or inhomogeneous low density lesion, the contrast-enhanced CT scan showed an enhanced density of the lesion during the arterial phase and a decreased density in the portal and delayed phases. Forty-four patients underwent the MRI examination; 10 of them were diagnosed with HAML (22.7%, 10/44). In these cases, the typical manifestation of the lesion showed a T1-weighted hypo-intensity (where the stripy hyper-intensity could be observed) and a T2-weighted hyper-intensity (Fig. 1). The Gadolinium-enhanced studies suggested that the lesions were enhanced in the arterial phase, and they still showed a slight enhancement in the portal and delayed phases.

Table II. The preoperative diagnostic established by US, CT and MRI

Diagnosis	US (94) n (%)	CT (70) n (%)	MRI (44) n (%)
HAML	0 (0%)	11 (15.7%)	10 (22.7%)
Hepatocellular carcinoma	15 (16.0%)	36 (51.4%)	18 (40.9%)
Hemangioma	10 (10.6%)	6 (8.6%)	1 (2.3%)
Lipoma	1 (1.1%)	1 (1.4%)	1 (2.3%)
Hamartoma	0 (0%)	4 (5.7%)	8 (18.2%)
Liposarcoma	0 (0%)	1 (1.4%)	0 (0%)
Focal nodular hyperplasia	0 (0%)	1 (1.4%)	2 (4.6%)
Benign tumor	68 (72.3%)	10 (14.3%)	4 (9.1%)



Fig 1. The typical MRI aspect of HAML.

Pathological study

Gross pathology of HAML showed usually a single, well-circumscribed and non-encapsulated tumor, consisting of soft to elastic tissue. The cutting surfaces of tumors were yellow-brown or dark-brown, some of them showed necrosis, hemorrhage and cystic degeneration (Fig. 2). In the microscopical evaluation, HAML showed a mixture of blood vessels, epithelia or spindle smooth muscle, and mature adipose tissue (Fig. 3). Epithelioid and spindle myoid cells formed vascular cuffing around the blood vessels, which was more often observed at the margin of tumor. Many thin wall veins or blood sinuses were diffused in the tumor parenchyma. Hematopoietic elements and inflammatory cell infiltration were often present within the tumors. A few eosinophilic hyaline globules and old pigment depositions could be observed within the cytoplasm. Tumor tissues occasionally evidenced an obvious invasion into the surrounding liver tissue with infiltrative border; however, no blood vessel invasion was found.

By immunohistochemistry study, all specimens (69/69, 100%) showed a strong and diffuse granular cytoplasmic

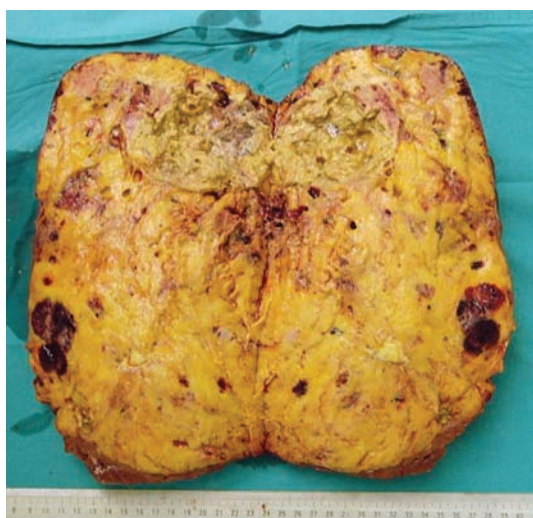


Fig 2. The gross pathology of the same patient after hepatectomy.

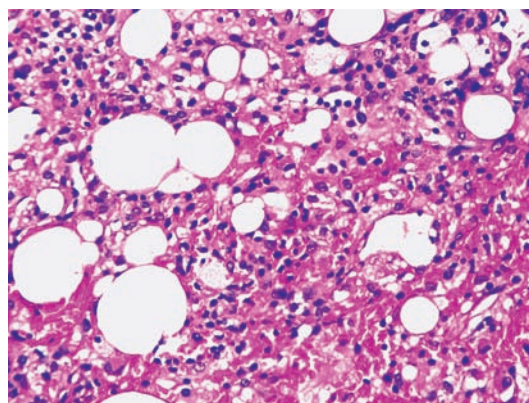


Fig 3. Tumor composed of adipose tissue, smooth muscle and blood vessels (H&E staining, x 200).

immunoreactivity for HMB-45 in epithelioid smooth cells, the spindle cells showed a weak immunostaining (Fig. 4).

CD34 was expressed in the endothelial cells of the capillary vessels, blood sinus and vessels, the positive rate was 75.3% (58/77). The positive rates for SMA, PCNA, CK18, and CK19 are shown in Table III. The immunostaining for AFP was negative in all specimens.

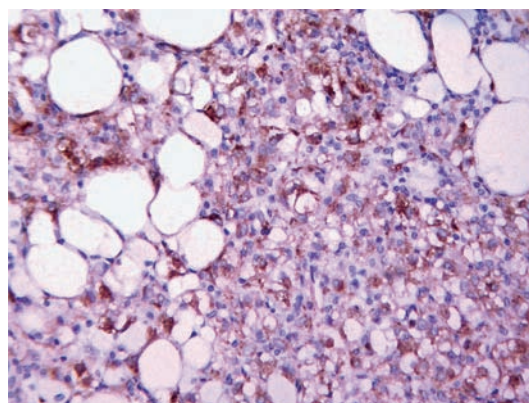


Fig 4. Tumor cells: immunohistochemical staining for HMB-45 (x 200).

Table III. The immunohistochemical study of the specimens

Antibody	Positive percentage n/total (%)
HMB45	69/69 (100%)
PCNA	42/52 (80.1%)
SMA	62/68 (91.2%)
CD34	58/77 (75.3%)
CK18	10/64 (15.6%)
CK19	1/63 (1.6%)

Treatment and follow-up

Ninety-three of the 94 patients were treated by hepatectomy, and one patient was treated with the ultrasound-guided radiofrequency ablation, having a tumor 2.5 cm in diameter, located in the right lobe and diagnosed through liver biopsy. All the patients were discharged from the hospital without postoperative complications. Among the

93 patients who underwent hepatectomy, 81 (86.2%) patients blocked the first portal hepatis (the average blocking time was 19.5 min) and 19 (20.4%) patients were given blood transfusion during the operation. The average volume of intraoperative blood loss and blood transfusion were 392 ml and 680 ml, respectively.

The follow-up study was completed for 86 patients (91.5%, 86/94) and the longest follow-up time was 10 years. No tumor recurrence or metastasis was found during the follow-up period.

Discussion

Angiomyolipomas are most frequently found in the kidneys and rarely in other organs such as the liver. Current research suggests that HAML is not a mesenchymal hamartoma but essentially a neoplasm that originates from perivascular epithelioid cells (PECs), which has a potential of multi-directional differentiation to vascular smooth muscle and epithelial cells [9]. According to the 2002 World Health Organization (WHO) classification of soft tissue tumors, renal and liver AML have been labeled as PEComas [10]. HAML is usually found in middle-aged women [5, 9]; in our series, the ratio of female to male was 2.6:1. The reason underlying this gender difference remains unknown. Using the immunohistochemistry method, Yeh et al [11] found that neither estrogen receptor (ER) nor androgen receptor (AR) is expressed in HAML, suggesting that sex hormones play no role in the pathogenesis and growth of HAML.

Up to now, the etiology and histogenesis of HAML is still unclear. Onset of the disease is concealed and most patients have no history of liver diseases and have no significant symptoms and specific signs. Some patients were detected by the imaging examination during a health check-up. The tumor markers AFP, CEA, CA19-9 were all negative. Most patients were diagnosed by a postoperative pathological examination. Yoshimura et al [12] showed a preoperative diagnostic accuracy for HAML of only 20%. In our study, the preoperative diagnostic accuracy of US, CT, and MRI were 0%, 15.7% and 22.7%, respectively. The imaging diagnosis is inaccurate mainly due to the various composition of HAML. The typical finding in CT examinations of mixed and myomatous type of HAML was that the contrast-enhanced CT scan of a lesion showed an irregular enhanced density during the arterial phase and a decreased density in the portal and delayed phases [12]. This feature of HAML in CT was similar to that of "fast-in-and-fast-out" tumor, characteristic of hepatocellular carcinoma (HCC). Thus, most patients were misdiagnosed as HCC preoperatively. The lipomatous type was frequently misdiagnosed as lipoma or liposarcoma; and the angiomatous type was misdiagnosed as hepatic hemangioma. In our series, we could often detect definite signals of adiposity using MRI. Sakamoto et al [13] found that HAML presented T1-weighted high-signal-intensity foci of adipose tissue, and after continuous strengthening for 6 min, this signal was obviously different from that of fatty metamorphosis. Hooper et al [14] proposed that the

technique of fat suppression can distinguish HAML from HCC.

To establish a preoperative diagnosis and avoid unnecessary resection, some investigators recommend fine-needle aspiration cytology (FNAC) to confirm the diagnosis of HAML [15]. However, HAML is composed of three tissues: blood vessels, smooth muscle and adipose cells. Different results may be drawn due to different puncture sites and as a result, it would be still challenging to diagnose HAML on the basis of FNAC.

The typical HAML pathological aspect is a varied mixture of blood vessels, epithelioid or spindle smooth muscle, and mature adipose tissue (Fig. 3). According to the line of differentiation and predominance of tissue components, Tsui et al [5] subcategorized HAML into mixed, lipomatous ($\geq 70\%$ fat), myomatous, and angiomatous types. The vessels abound in branches and are often thick-walled arteries and thin-walled sinusoids. There is an irregular thickening accompanied with homogeneous and erythro-stained depositions in larger arteries. The immunohistochemical characteristic of HAML is that epithelioid smooth cells show a strong and diffuse granular cytoplasmic immunoreactivity for HMB-45, a melanoma cell differentiation-associated marker. The spindle cells showed a weak immunostaining for HMB-45. According to the Jungbluth et al [16] study the HMB-45 mRNA is expressed in smooth cells, the immunostaining is specific and not generated by cross-reactions. In our study, all the 69 cases immunostained with HMB-45 showed positive reaction; the same results were found by Makhoul et al [17]. Our results suggest that drawing multiple materials from the three HAML components is helpful to confirm the diagnostic result. Since no other primary hepatic tumors are immunoreactive with HMB-45, the HMB-45 immunostaining can lead to the definitive diagnosis of HAML.

At present, more attention should be paid to the biological behavior of HAML. Since HAML was once thought to be benign, asymptomatic and growing slowly, some researchers recommended non-operative management with close follow-up after diagnosis, and surgical intervention performed only when clinical symptoms appeared [6]. In 2000, Dalle et al [8] reported the first case of HAML with malignant vessel invasion and multiple metastases in the residual liver. Since then, more recurrent cases after surgical resection have been reported [18, 19]. On the other hand, Chang et al [20] reported one case of HAML with two concomitant HCCs on a hepatitis B carrier, whose pathological findings showed a typical angiomyolipoma and two well-differentiated HCCs with marked fatty metamorphosis. Therefore, nonsurgical treatment of angiomyolipoma in an endemic area for HCC should proceed with caution. Among our patients, we found two cases where the tumor grew faster. One of them underwent MRI examination and showed an 8x7 cm HAML lesion in the right lobe at the first visit. After one-year of close observation, the size of tumor became 27x17 cm, and the patient had symptoms of abdominal discomfort. Finally, the patient underwent surgical intervention, because the

increase of the tumor-size would have significantly increased the risk of operation.

Since HAML has a potential for malignant transformation and a risk of spontaneous rupture as well as a concomitant HCC, surgical intervention should be considered as the treatment of choice once the diagnosis is confirmed. In our experience, if the tumor is smaller than 5 cm and the tumor location is far from the gastrointestinal tract, large bile ducts and large blood vessels, radiofrequency ablation may be a good choice for the HAML treatment, where the electrodes generate heat and destroy tumor cells thoroughly. If the tumor is larger than 5 cm, surgical intervention should be considered as the primary treatment choice. Since HAML seldom forms fibrous capsules, we suggest the excision extension including the whole tumor and part of surrounding normal tissues to avoid the residue of tumor tissues. Yang et al [9] reported a case recurrence six months after surgical dissection and suggested that the main reason for recurrence was the residual tumor tissue in the cutting margin. So the operation staff should manipulate gently and avoid squeezing tumor tissues during the operation.

Conclusion

There are no specific signs and symptoms of HAML. The preoperative imaging tests (including CT, MRI) are insensitive. The common pathological features include the basic histological components and expression of HMB-45. The surgical resection should be considered as a treatment choice for HAML.

Authors' contributions

Zhi-Gang Chang and Jin-Ming Zhang designed the research, Zhi-Gang Chang and Jin-Ming Zhang performed the research, Zhi-Gang Chang, Jin-Ming Zhang, Jiao-Qian Ying, and Yu-Ping Ge gathered in the patients. Zhi-Gang Chang and Jin-Ming Zhang analyzed the data and wrote this paper.

Conflicts of interest

No conflicts of interest have been declared by all authors.

References

1. Ishak KG. Mesenchymal tumors of the liver. In: Okuda K, Peters RL, eds. *Hepatocellular Carcinoma*. New York: John Wiley & Sons, 1976
2. Ji Y, Zhu X, Xu J, et al. Hepatic angiomyolipoma: a clinicopathologic study of 10 cases. *Chin Med J (Engl)* 2001;114:280-285.
3. Li T, Wang L, Yu HH, et al. Hepatic angiomyolipoma: a retrospective study of 25 cases. *Surg Today* 2008;38:529-535.
4. Ren N, Qin LX, Tang ZY, Wu ZQ, Fan J. Diagnosis and treatment of hepatic angiomyolipoma in 26 cases. *World J Gastroenterol* 2003;9:1856-1858.
5. Tsui WM, Colombari R, Portmann BC, et al. Hepatic angiomyolipoma: a clinicopathologic study of 30 cases and delineation of unusual morphologic variants. *Am J Surg Pathol* 1999;23:34-48.
6. Yeh CN, Chen MF, Hung CF, Chen TC, Chao TC. Angiomyolipoma of the liver. *J Surg Oncol* 2001;77:195-200.
7. Nguyen TT, Gorman B, Shields D, Goodman Z. Malignant hepatic angiomyolipoma: report of a case and review of literature. *Am J Surg Pathol* 2008;32:793-798.
8. Dalle I, Sciot R, de Vos R, et al. Malignant angiomyolipoma of the liver: a hitherto unreported variant. *Histopathology* 2000;36:443-450.
9. Yang CY, Ho MC, Jeng YM, Hu RH, Wu YM, Lee PH. Management of hepatic angiomyolipoma. *J Gastrointest Surg* 2007;11:452-457.
10. Christopher DM, Fletcher K, Krishnan U, Fredrik E. *Pathology and Genetics of Tumors of Soft Tissue and Bone*. IARC Press: Lyon, 2002: 222.
11. Yeh CN, Lee KF, Chen MF. Immunohistochemical study of hepatic angiomyolipoma. *Hepatogastroenterology* 2005;52:1151-1153.
12. Yoshimura H, Murakami T, Kim T, et al. Angiomyolipoma of the liver with least amount of fat component: imaging features of CT, MR, and angiography. *Abdom Imaging* 2002;27:184-187.
13. Sakamoto Y, Inoue K, Ohtomo K, Mori M, Makuuchi M. Magnetic resonance imaging of an angiomyolipoma of the liver. *Abdom Imaging* 1998;23:158-160.
14. Hooper LD, Mergo PJ, Ros PR. Multiple hepatorenal angiomyolipomas: diagnosis with fat suppression, gadolinium-enhanced MRI. *Abdom Imaging* 1994;19:549-551.
15. Al Nazer M, Ashraf MA. Fine-needle aspiration cytology of hepatic angiomyolipoma: case report with histological, immunohistochemical and electron microscopic findings. *Ann Saudi Med* 2001;21:324-333.
16. Jungbluth AA, Iversen K, Coplan K, et al. Expression of melanocyte-associated markers gp-100 and Melan-A/MART-1 in angiomyolipomas. An immunohistochemical and rt-PCR analysis. *Virchows Arch* 1999;434:429-435.
17. Makhoul HR, Ishak KG, Shekar R, Sesterhenn IA, Young DY, Fanburg-Smith JC. Melanoma markers in angiomyolipoma of the liver and kidney: a comparative study. *Arch Pathol Lab Med* 2002;126:49-55.
18. Croquet V, Pilette C, Aubé C, et al. Late recurrence of a hepatic angiomyolipoma. *Eur J Gastroenterol Hepatol* 2000;12:579-582.
19. Flemming P, Lehmann U, Becker T, Klempnauer J, Kreipe H. Common and epithelioid variants of hepatic angiomyolipoma exhibit clonal growth and share a distinctive immunophenotype. *Hepatology* 2000;32:213-217.
20. Chang YC, Tsai HM, Chow NH. Hepatic angiomyolipoma with concomitant hepatocellular carcinomas. *Hepatogastroenterology* 2001;48:253-255.