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· 专题研究 ·

肝脏血管平滑肌脂肪瘤诊断与外科治疗：附19例报告

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摘要

背景与目的: 肝脏血管平滑肌脂肪瘤(HAML)是肝脏少见的一种间叶组织来源的良性肿瘤,影像学检查缺乏特异性,术前诊断率低,容易误诊为肝细胞癌或其他肝良性肿瘤,本文报告19例HAML患者的诊治过程,以期为临床提供参考和借鉴。

方法: 回顾性分析2011年1月—2019年12月收治的19例HAML患者临床资料,其中女12例,男7例;年龄28~61岁;体检发现无临床症状者14例,表现为上腹部隐痛者3例,间断腹胀者1例,腹痛伴腹泻者1例;1例合并慢性乙型病毒性肝炎及肺脓肿,1例合并乙型肝炎肝硬化代偿期。19例均不伴肾肺等其他脏器血管平滑肌脂肪瘤,均无结节性硬化症。肿瘤直径1.3~12 cm,平均直径(4.6±2.2) cm。AFP、CA19-9、CEA均正常。7例患者术前诊断肝细胞癌(36.8%),12例术前诊断肝良性肿瘤(63.2%),分别为7例诊断肝腺瘤,2例诊断炎性假瘤,1例诊断肝海绵状血管瘤,1例诊断肝局灶性结节性增生,1例术前行超声引导下肝脏穿刺活检病理证实HAML。

结果: 患者均行外科手术治疗,18例行肝切除治疗,1例行超声引导下肝肿瘤穿刺活检术、经皮穿刺肝肿瘤射频消融术。平均手术时间(172.7±80.4) min,术中平均出血量为(456.6±528.1) mL,平均术后住院时间(9.8±2.7) d。19例患者病理检查均证实HAML,其中7例为上皮样血管平滑肌脂肪瘤,免疫组化检查HMB-45、SMA均阳性表达。患者术后恢复良好,所有患者无肝衰竭、腹腔出血、胆汁漏等并发症发生,无死亡病例。全部病例均获随访,均未发现肿瘤复发及转移。术后患者有良好的生活质量。

结论: HAML瘤属于良性肿瘤,术前诊断比较困难,一部分患者容易误诊为肝细胞癌,最终诊断依靠病理及免疫组织化学染色,外科手术切除是安全、有效的治疗选择,预后良好。

关键词

肝肿瘤; 血管肌脂瘤; 肝切除术

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Diagnosis and surgical treatment of hepatic angiomyolipoma: a report of 19 cases

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Abstract

Background and Aims: Hepatic angiomyolipoma (HAML) is a rare benign mesenchymal tumor of the

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liver, with no specific imaging features and low preoperative diagnosis rate. It is frequently misdiagnosed as hepatocellular carcinoma (HCC) or other hepatic benign tumors. This article reports the diagnosis and treatment process of 19 patients with HAML, so as to provide a reference and guidance for clinical practice.

Methods: The clinical data of 19 cases with HAML treated from January 2011 to December 2019 were retrospectively analyzed. Of the patients, 12 cases were females and 7 cases were males, with the age ranging from 28 to 61 years; lesion was found by health maintenance examination in 14 cases without clinical symptoms, 3 cases had abdominal pain, one case had intermittent abdominal distention, and one case had abdominal pain and diarrhea; one case was complicated with chronic hepatitis B and pulmonary abscess, one case was complicated with liver cirrhosis in compensatory period. All the 19 patients did not have angiomyolipoma of other organs such as kidney and lung, and none of them had tuberous sclerosis. The diameter of the tumors ranged from 1.3 to 12 cm, with an average diameter of (4.6 ± 2.2) cm. The levels of AFP, CA19-9 and CEA were all within the normal range. Seven patients (36.8%) were diagnosed as HCC before operation, and 12 patients (63.2%) were considered as hepatic benign tumors that included 7 cases were diagnosed as hepatic adenoma, 2 cases were diagnosed as inflammatory pseudotumor, one case was diagnosed as hepatic cavernous hemangioma, one case was diagnosed as hepatic focal nodular hyperplasia, and one case was identified as HAML by preoperative ultrasound guided liver biopsy pathology.

Results: All patients underwent surgical treatment, including hepatic resection in 18 patients and ultrasound guided liver tumor biopsy and percutaneous puncture radiofrequency ablation of the liver tumor in one patient. The average operative time was (172.7 ± 80.4) min, intraoperative blood loss was (456.6 ± 528.1) mL, and length of hospital stay was (9.8 ± 2.7) d. HAML was confirmed in all the 19 patients by pathological examination, in which seven cases were epithelioid angiomyolipoma. HMB-45 and SMA were positive in immunohistochemical staining. All patients recovered well after operation, and no complications such as liver failure, abdominal bleeding and bile leakage as well as death occurred. All patients were followed up, and no tumor recurrence and metastasis were found. All patients had good quality of life.

Conclusions: HAML belongs to benign tumor, and is difficult to diagnose before operation. Some patients were easily misdiagnosed as HCC. The final diagnosis depends on pathological and immunohistochemical analysis. Surgical resection is a safe and effective treatment option with good prognosis.

Key words Liver Neoplasms; Angiomyolipoma; Hepatectomy

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肝脏血管平滑肌脂肪瘤 (hepatic angiomyolipoma, HAML) 是肝脏少见的一种间叶组织来源的良性肿瘤, 该病发病率低, 大多数患者临床上无自觉症状, 影像学表现多样性, 缺乏特异性, 术前诊断正确率低, 术前容易误诊为肝癌或其他肝良性肿瘤^[1]。为了提高对该病的认识水平及诊断率, 减少临床误诊, 笔者收集解放军总医院第五医学中心肝胆外科自 2011 年 1 月—2019 年 12 月手术治疗的 HAML 患者临床资料, 共有 19 例 HAML, 现分析如下。

1 资料与方法

1.1 一般资料

本组 19 例 HAML 患者均接受外科手术治疗, 并行病理及免疫组化最终确诊为 HAML, 其中女 12 例, 男 7 例; 年龄在 28~61 岁, 平均 (46.5 ± 7.5) 岁。常规体检发现无临床症状者 14 例, 表现为上腹部隐痛者 3 例, 间断腹胀者 1 例, 腹痛伴腹泻者 1 例。1 例肿瘤多发, 18 例为单发。其中 1 例合并慢性乙型病毒性肝炎及肺脓肿, 1 例合并乙型肝炎

肝硬化代偿期, 1例合并膀胱癌及甲状腺功能亢进, 1例有长期大量饮酒史, 1例曾有口服中药史。19例均不伴肾肺等其他脏器血管平滑肌脂肪瘤, 均无结节性硬化症(TSC)。肿瘤直径1.3~12 cm, 平均直径(4.6±2.2) cm。肿瘤部位: 位于肝右叶8例, 左叶9例, 单侧尾状叶1例, 左右尾状叶1例。

1.2 血清学检查

9例患者术前查血常规无明显异常, 肝功基本正常, 凝血酶原时间、活动度均正常。肿瘤标记物AFP、CEA、CA19-9均正常。2例HBsAg呈阳性, 1例HBV-DNA<40 IU/mL, 1例HBV-DNA 3.66×10³ IU/mL。

1.3 影像学检查

其中15例患者行肝脏超声检查, 显示病灶实性, CDFI示可见束状血流信号, 内部回声不均匀, 7例表现为高回声团块, 8例表现为低回声团块(图1)。2例行肝脏超声造影检查考虑肝良性肿瘤。11例行肝脏增强CT检查, 平扫病变均呈低密

度影, 增强扫描动脉期出现强化, 6例门脉期及延迟期造影剂有所消退呈现低密度影(图2), 5例门脉期及延迟期仍有强化。18例行肝脏增强MRI检查, 病灶均表现为长T1长T2信号, 内见脂质信号, 增强扫描动脉期均出现强化, 11例门脉期及延迟期造影剂有所消退呈稍低信号, 7例门脉期及延迟期仍强化呈稍高信号或等信号(图3)。其中1例行增强MR特异性造影剂普美显检查, 显示肝S5病灶呈长T1稍长T2信号, 动脉期病灶明显强化, 门脉期呈等信号, 肝胆期(20 min)呈低信号, 考虑为肝细胞癌。

1.4 术前诊断

7例患者术前诊断肝细胞癌(36.8%), 12例术前诊断肝良性肿瘤(63.2%): 7例诊断肝腺瘤, 2例诊断炎性假瘤, 1例诊断肝海绵状血管瘤, 1例诊断肝局灶性结节性增生, 1例术前行超声引导下肝脏穿刺活检病理证实血管平滑肌脂肪瘤。

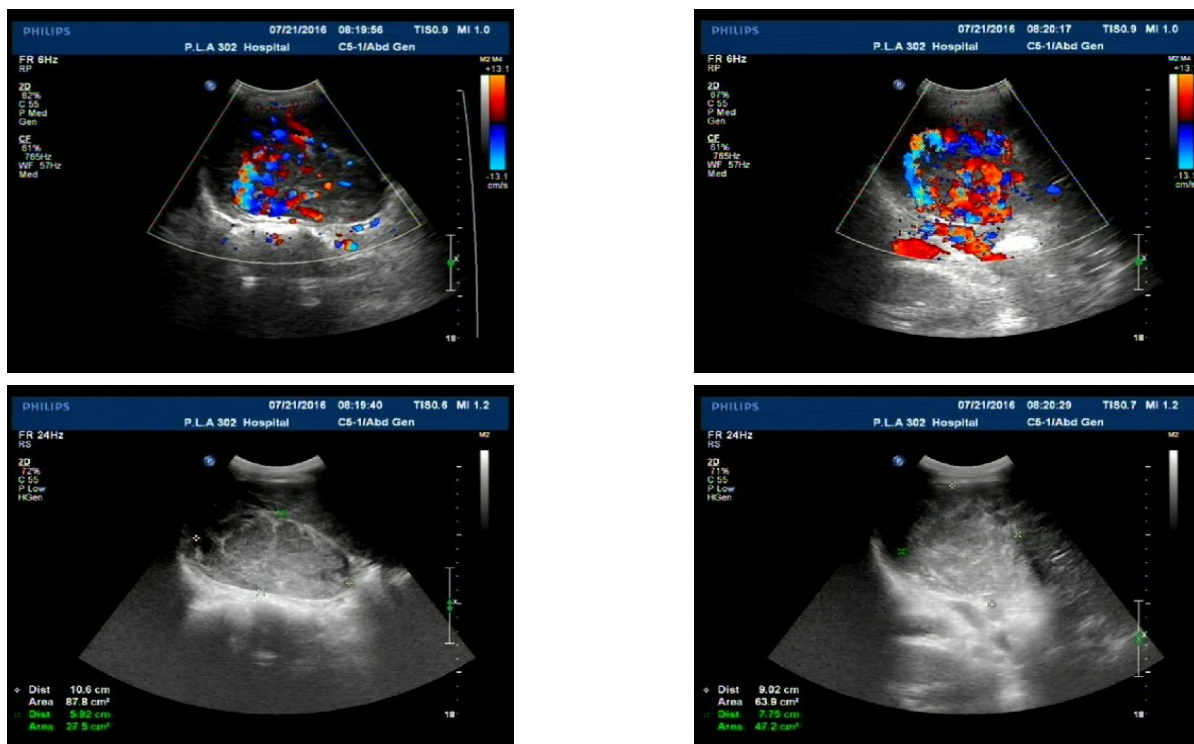


图1 腹部超声示: 肝右叶不均质低回声团块, 范围约106 mm×59 mm, CDFI示血流信号极丰富

Figure 1 Abdominal ultrasound showing irregular hypoechoic mass in the right liver, with a range about 106 mm×59 mm, and strong CDFI blood flow signal

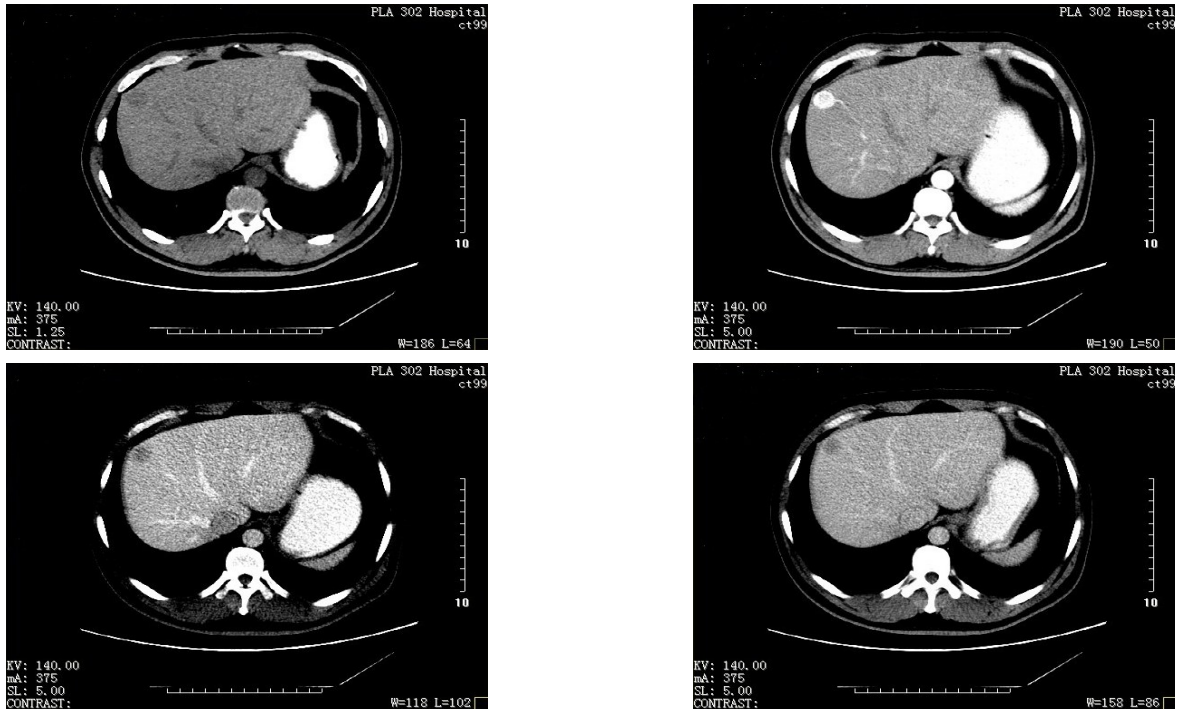


图2 肝脏增强CT三期扫描示：肝右前叶富血供占位性病变，直径约1.5 cm，平扫呈低密度影，动脉期病灶明显均匀强化，并见肝动脉分支供应肿瘤，门脉期及延迟期病灶内造影剂消退，呈“快进快出”特点

Figure 2 Enhanced CT three-phase scanning showing a blood-rich space-occupying lesion in the right anterior lobe of the liver, with diameter of 1.5 cm, low-density shadow in the plain scan, significant uniform enhancement of the lesion in arterial phase, and hepatic artery branch supplying the tumor, and contrast agent in the lesion vanishing in portal-venous phase, characterized by a phenomenon of “rapid entry and rapid removal”

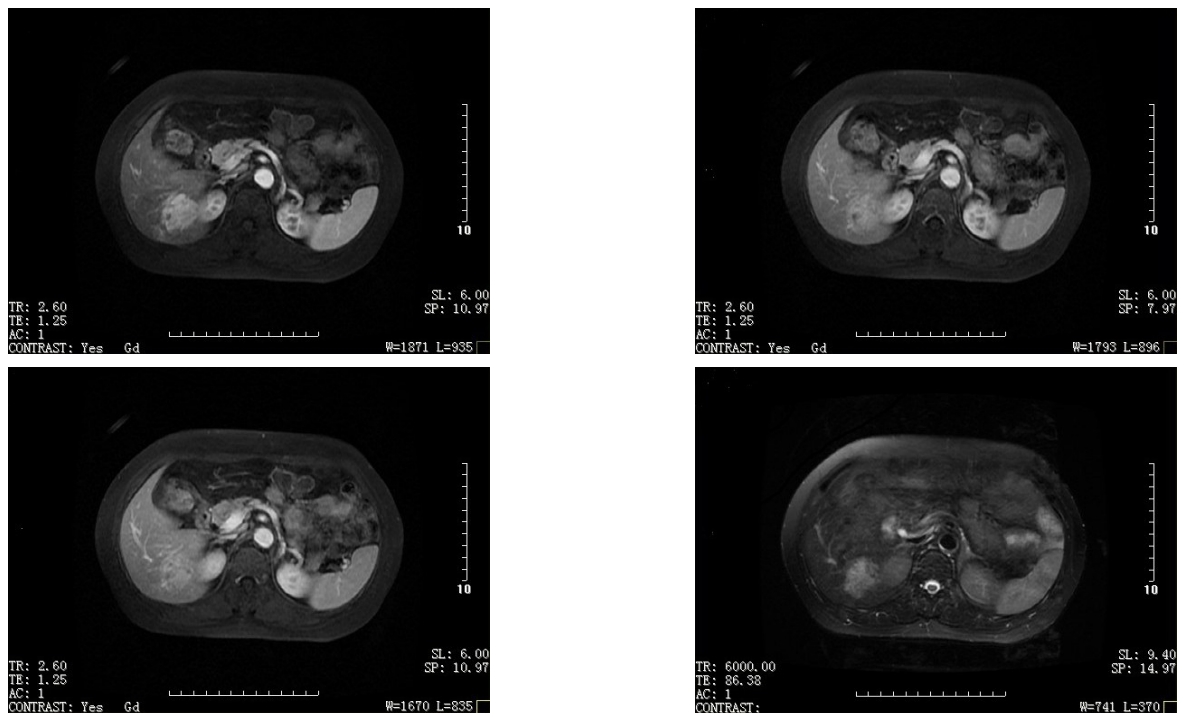
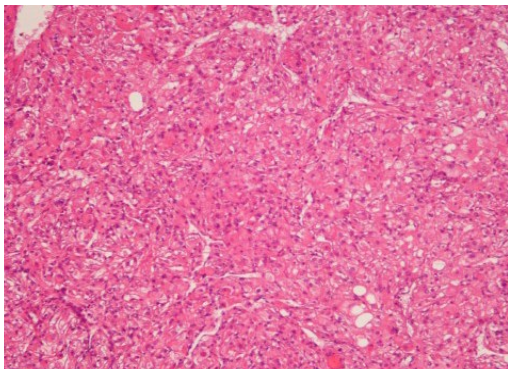


图3 肝脏增强MRI示肝S6内缘占位，增强扫描动脉期病变明显不均匀强化，门脉期及延迟期呈等或稍高信号

Figure 3 Enhanced MRI showing space-occupying lesion in the inner-edge of the S6 segment of the liver, with significantly heterogeneous enhancement of the lesion during arterial phase, and equal or slightly high signal intensity during portal-venous and delayed phases

1.5 治疗方法

本组19例患者均获手术治疗:18例行肝切除术,其中6例行腹腔镜肝切除术(腹腔镜下肝S6切除术,腹腔镜下肝S5肿瘤切除术,腹腔镜肝右后叶肿瘤切除术,腹腔镜下胆囊切除术+肝S4肿瘤切除术,腹腔镜下肝左外叶切除术,腹腔镜下胆囊切除术+左半肝切除术),1例行机器人辅助下肝左外叶切除术;12例行开腹肝切除术,其中1例左侧尾状叶巨大肿瘤行左侧尾状叶切除术,1例左右尾状叶多发肿瘤行左半肝切除术+左尾状叶切除术+右尾状叶肿瘤切除术,1例患者合并代偿期的乙型肝炎肝硬化,肿瘤巨大与大网膜、腹壁及右肾粘连重行腹腔粘连松解+肝右后叶切除术,1例行超声引导下肝肿瘤穿刺活检术+经皮穿刺肝肿瘤射频消融术。患者平均手术时间(172.7±80.4)min,术中平均出血量为(456.6±528.1)mL,平均术后住院时间(9.8±2.7)d。



2 结果

2.1 病理及免疫组织化学染色结果

19例患者病理均确诊为HAML(图4),其中7例上皮样血管平滑肌脂肪瘤,1例上皮样血管平滑肌脂肪瘤伴出血,呈浸润性生长,倾向恶性。肉眼观:肿瘤剖面呈暗红色或黄白色,实性,质软,大多数边界较清但无完整包膜,少数可伴有出血坏死。镜下肿瘤由血管、平滑肌细胞以及脂肪细胞以不同比例混合组成,可伴少量炎细胞浸润。免疫组化检查表达阳性的为黑色素特异性抗体HMB-45 100%(19/19)、平滑肌肌动蛋白(SMA) 100.0%(17/17)、CD34 100.0%(19/19)、波形蛋白(vimentin) 61.5%(8/13)、S-100 16.7%(2/12)、CD117 14.3%(2/14)(表1)。而Hepatocyte、AFP、CEA、GPC-3、CD10、CK7、CK19表达均阴性。

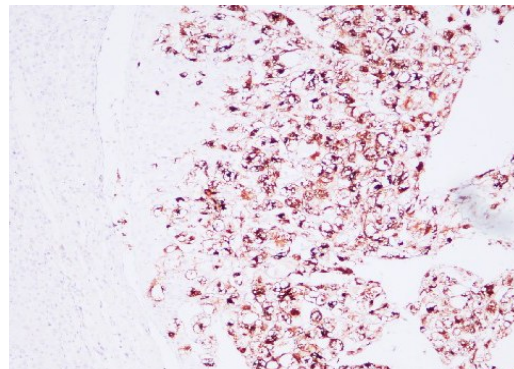


图4 病理证实肝脏上皮样血管平滑肌脂肪瘤,肿瘤由血管、平滑肌细胞、脂肪细胞组成;免疫组化:HMB-45染色阳性(++),SMA(+),CD34(血管化+),vimentin(+),CD117(-),Hepa(-),GPC-3(-),CD10(-),AFP(-)

Figure 4 Pathology showing the epithelioid angiomyolipoma of the liver, consisting of vascular cells, smooth muscle cells and fat cells; immunohistochemistry showing HMB-45(++), SMA(+), CD34(+), vimentin(+), CD117(-), Hepa(-), GPC-3(-), CD10(-), and AFP(-)

表1 19例HAML免疫组化染色分析

Table 1 Analysis of immunohistochemical staining analysis of 198 cases of HAML

抗体表达	(+)	(++)	(+++)	(-)	阳性率(%)
HMB45	8	10	1	0	100.0(19/19)
SMA	12	5	0	0	100.0(17/17)
CD34	15	4	0	0	100.0(19/19)
vimentin	8	0	0	5	61.5(8/13)
S-100	2	0	0	10	16.7(2/12)
CD117	2	0	0	12	14.3(2/14)

2.2 预后及随访

患者术后恢复良好,其中1例患者术后第6天因肝周局限性积液行彩色超声引导下腹腔穿刺置管引流术,出院前拔除腹腔引流管。本组所有患者均无肝衰竭、腹腔出血、胆汁漏、严重感染等并发症发生,均无二次手术,无死亡病例。全部病例均获随访,随访时间6个月至8年,影像学检查均未发现肿瘤复发及转移。术后患者临床症状消失,有良好的生活质量及精神状态。

3 讨论

3.1 病因及发病机制

血管平滑肌脂肪瘤 (angiomyolipoma, AML) 常见于肾脏, 肝脏少见, 其病因和发病机制尚不完全清楚。目前研究认为该肿瘤细胞起源于血管周上皮样细胞 (perivascular epithelioid cell, PEC), 属于一种血管周上皮样细胞肿瘤 (PEComa), 具有多向分化潜能, 可向血管平滑肌和上皮细胞分化的间叶组织的良性肿瘤并表达黑色素瘤相关的抗体^[2-4]。肝脏及肾脏血管平滑肌脂肪瘤的发生可能与 TSC2 基因突变有关^[5-6], Jimenez 等^[7]研究也发现肾脏血管平滑肌脂肪瘤发生与结节性硬化症密切相关, 但单发的肝脏血管肌脂肪瘤一般不合并 TSC^[8]。本组 19 例患者中 18 例肿瘤单发, 1 例左右尾状叶多发, 均未发现合并结节性硬化症。

3.2 临床特点与诊断

HAML 多见于中青年女性, Klompenhouwer 等^[9]检索分析 292 例 HAML, 男女比例约为 1:3。大多数患者在健康体检时发现, 无明显的临床症状, 少部分患者随着肿瘤的增大出现上腹部隐痛或腹胀等不典型症状, 也有极少数患者以不明原因的发热甚至高热起病, 临床上易误诊为肝脓肿^[10]。或患者检查治疗其他疾病时发现, 本组中 1 例患者在治疗肺部脓肿时检查发现肝脏肿瘤而就诊我科。与肝细胞癌不同, 该病绝大多数患者无病毒性肝炎、酒精性或药物性肝炎及肝硬化病史, 病灶多单发, 肝癌标记物 AFP 正常。

HAML 由不同比例的血管、平滑肌和脂肪细胞组成, Tsui 等^[11]根据肿瘤内组织成分的差异把 HAML 分为 4 型: 混合型 (经典型)、脂肪型 (脂肪 $\geq 70\%$)、平滑肌型 (脂肪 $\leq 10\%$)、血管型, 其中混合型最常见。在影像学诊断方面, 目前彩色超声、增强 CT 及 MRI 等检查缺乏特异性, 检查诊断率较低, 有时很难与肝癌或其他良性肿瘤鉴别。由于肿瘤内组织成分不同, HAML 的声像图具多样性, 可呈高回声或混合回声, 也可呈低回声, 其中上皮样 HAML 则以低回声表现为主, 内部回声多不均匀, CDFI 示周边及内部可见较明显束状血流信号, 显示肿瘤血供丰富, 超声造影表现均匀高增强、快进不退或慢退为主^[12]。结合肝脏超声造影更加直观的动态观察肿瘤的血流分布及微气泡造影剂三期灌注过程, 为鉴别肿瘤的良好性提供更

准确的信息。有报道^[13]超声造影对 HAML 的诊断准确率优于增强 CT 及 MRI。本组 2 例行肝脏超声造影检查均考虑良性肿瘤, 但其中 1 例行增强 CT 检查则考虑肝癌, 超声造影诊断率优于 CT。笔者建议更多患者术前行超声造影检查, 从而更有利于临床医生做出准确的判断。最近 Naito 等^[14]研究认为超声瘤内表现高回声光团、网状结构特征可以帮助区分 HAML 和肝细胞癌。

本组患者更多的是采用增强 CT 及 MRI 检查: 肿瘤 CT 平扫为低密度影, MR 为长 T1 长 T2 信号, 病灶内见脂质成分, 加脂肪抑制后病灶信号降低。CT 和 MR 重要表现是富血供肿瘤伴有动脉期供血动脉的显示^[15], 因此增强扫描 HAML 在动脉期均出现不同程度的强化^[16], 有的肿瘤在门脉期及延迟期仍强化, 表现为“快进慢出”特点, 容易误诊为肝血管瘤、肝局灶性结节性增生、肝腺瘤等; 有的肿瘤在门脉期及延迟期造影剂消退, 呈“快进快出”特点, 容易误诊为肝细胞癌。本组 11 例患者行增强 CT 检查, 5 例诊断肝癌, 占 45.5%, 18 例行增强 MR 检查, 7 例诊断肝癌, 占 38.9%, 误诊率低于 CT。目前研究发现 HAML 在影像学上也有较典型表现: 有早期引流的肝静脉, 瘤内有脂肪成分, 肿瘤多血管性, MRI 动脉期强化明显, 门脉期仍中低度强化、DWI 表现为等信号^[17-19], 这些特征可以更好地帮助我们与肝细胞癌鉴别。

确诊 HAML 最终依靠术后病理及免疫组织化学染色。显微镜下可见肿瘤由 3 种成分组成: 血管、平滑肌和脂肪细胞。丛文铭等^[20]根据瘤细胞形态分为上皮样细胞型、中间细胞型、梭形细胞型、单形性细胞型 (嗜酸细胞型) 及多形性细胞型。免疫组织化学染色肿瘤细胞阳性表达 HMB-45、Melan-A、SMA 是诊断 HAML 的可靠证据^[21-23]。本组患者 HMB-45 阳性表达率 100%、SMA 为 100%、vimentin 为 61.5%, 而 S-100 及 CD117 阳性率低。19 例患者血管内皮标记 CD34 均见阳性表达, 显示此肿瘤富血管。Ki-67 作为细胞增殖指数, 与肿瘤恶性程度成正相关, 越高表示肿瘤细胞增殖多, 恶性程度也越高, 本组 19 例患者免疫组化显示 Ki-67 数值低, 提示此肿瘤处于低增殖状态。

在临床上还应该注意 HAML 几个特点: (1) HAML 虽然在本质上是良性, 但有恶性转化, 极少数 HAML 会出现恶变, 主要发生在上皮样亚型^[24]。Deng 等^[25]报道 HAML 恶性特征有细胞异型性、血管

侵犯、高增殖活性(Ki-67指数高于30%)和大肿瘤。(2)肝细胞癌合并HAML同时出现^[26], Ge等^[27]报告1例无肝硬化背景的男性患者肝细胞癌同时合并HAML及肝脏海绵状血管瘤,使得HAML的术前诊断更加复杂。(3)HAML有自发破裂出血的风险^[28]。

3.3 临床治疗及预后

外科手术是治疗本病最为有效的手段,手术方法根据肿瘤位置及大小可选择肝切除、局部消融等。Klompshouwer等^[9]检索分析292例HAML,其中有247例接受了外科手术切除治疗,国内学者Yang等^[29]也报道了92例HAML,其中有68例接受了肝切除术,22例接受射频消融术,从这些多样本病例中可发现绝大多数患者行外科手术切除治疗。本组19例患者肿瘤平均直径(4.6±2.2)cm,其中有18例行肝切除治疗,1例2.3cm肿瘤的行超声引导下肝肿瘤穿刺活检术+肝肿瘤射频消融术。患者术后均恢复良好,无腹腔出血、胆漏、肝衰竭、严重感染等并发症发生,无死亡病例,笔者认为通过肝切除或局部消融,手术安全有效,预后良好,其中手术切除是首选,可以完整的切除病灶,有效的保证切缘阴性,减少肿瘤的再复发,尤其是直径超过3cm的肿瘤。

余锋等^[30]指出肝切除术是治疗HAML的理想方法,建议肿瘤>5cm、位于肝中叶或尾状叶、有临床症状及肿瘤生长较快者选择手术。基于以下几点考虑,笔者认为HAML应当积极采取手术治疗,肝切除是首选^[31-32]:(1)HAML血供丰富,肿瘤越大,尤其是位于尾状叶、肝中叶等特殊部分的大肿瘤,后续手术切除难度会明显增加,术中出血量也增加,并发症发生率也高。本组1例患者左侧尾状叶巨大肿瘤行肝左尾状叶切除术,1例左右尾状叶多发肿瘤行左半肝切除术、左尾状叶切除术、右尾状叶肿瘤切除术,术中出血量均超过2000mL。(2)HAML有恶变风险,尤其是上皮样血管平滑肌脂肪瘤,本组有1例青年女性患者肿瘤直径约2.6cm,病理为上皮样血管平滑肌脂肪瘤,浸润性生长,倾向恶性,所以不能单纯以肿瘤大小决定恶变风险及手术时机。(3)部分HAML影像学表现类似于肝细胞癌,两者术前鉴别诊断困难,保守治疗有可能将真正的肝癌当成HAML而漏诊。(4)HAML有自发破裂出血的风险,尤其是外生性肿瘤。因此早一步行手术切除不仅能明确诊断,也能及早预

防肿瘤癌变出血等风险。此外,少数外生性大肿瘤可能与周围组织粘连,增加手术难度及出血量,本组1例患者肝S6外生性肿瘤,与大网膜、腹壁及右肾被膜粘连重,分离困难,术中出血较多,手术时间较长。因此结合笔者的经验,因肿瘤血供丰富,尤其是巨大肿瘤,术中避免过度挤压以免造成肿瘤破裂出血,尤其是肝尾状叶或肝中叶等特殊部分的肿瘤,术前应做好充分评估及备血。

随着外科医生腹腔镜技术的进步,一些部位的肿瘤可通过腹腔镜下肝切除^[33]或机器人辅助下肝切除治疗,本组有6例患者行腹腔镜下肝切除术,1例行机器人辅助下肝左外叶切除术,术中出血量较少,术后恢复快,住院时间缩短,安全有效。≤3cm的肿瘤或高龄患者也可选择行穿刺活检+肿瘤局部消融术。恶性HAML切除术后复发也可行肝移植治疗^[34]。

综上所述,HAML属于良性肿瘤,术前诊断较困难,成像特点类似于肝细胞癌,最终诊断依靠病理及免疫组织化学染色。外科手术切除是安全、有效的首选治疗选择,可以获得良好的疗效,有效减低再复发几率。在临床工作中要提高对该病的认识水平,意识到潜在的恶变和破裂出血的风险,建立长期门诊随访程序,及早进行有效合理的外科手术治疗。

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