Malignant potential of epithelioid angiomyolipomas of the liver: A case report and comprehensive review of the literature

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Abstract. Hepatic epithelioid angiomyolipoma (HEAML) is a rare mesenchymal tumor that has been reported to have malignant potential. We herein describe a rare case of atypical HEAML. A 43-year-old Caucasian male patient visited his general practitioner due to a productive cough persisting for >2 months. During evaluation with several imaging tests, a chest computed tomography (CT) incidentally revealed a well-demarcated lesion in the caudate lobe of the liver, sized 7 cm. An abdominal magnetic resonance imaging examination confirmed the findings of the CT. The possibility of hepatocellular carcinoma at that time could not be excluded. Due to inconclusive cross-sectional imaging, the patient underwent left hepatectomy with additional resection of segment I. The patient's postoperative course was uneventful. A diagnosis of 'atypical' HEAML was established in the present case. The majority of HEAMLs are considered to be benign, although there are several reported cases exhibiting malignant behavior, such as tumor growth, presence of atypical cells, recurrence after surgical resection, metastasis and invasive growth into the liver parenchyma and alongside the vessels. From 2000 onwards, 19 cases of malignant hepatic AML have been reported. Malignant transformation is considered to occur mostly in the epithelioid subtype. To that end, when epithelioid or atypical characteristics are identified on preoperative biopsy, resection is indicated due to the high probability of malignancy.

Introduction

Angiomyolipomas (AMLs) are rare mesenchymal solid tumors that consist of variable proportions of adipose tissue, smooth muscle cells and blood vessels. In 2002, AMLs were included in perivascular epithelioid cell neoplasms (PEComas) by the World Health Organization (1,2). According to the dominant cell type, AMLs maybe further divided into epithelioid, spindle-cell and intermediate subtypes. AMLs are usually benign tumors, most often encountered in the kidney, whereas the liver is the most frequent extrarenal site. Extrarenal occurrence of AML is quite uncommon, with ~600 cases of hepatic AMLs reported in the literature to date (3). Hepatic epithelioid AML (HEAML) is a particular type of AML that was first reported by Yamasaki *et al* in 2000 (4), with no more than 80 cases reported worldwide to date (5). HEAML, which was generally considered to be benign in the past, has malignant potential according to several reports (6). However, the natural history of this type of tumor has not yet been elucidated. There are no pathognomonic clinical, laboratory or radiological characteristics of HEAML; thus, it may easily be mistaken for other types of hepatic tumors, and the rate of misdiagnosis is very high.

A small number of reported cases exhibit malignant characteristics, such as invasive growth pattern, vascular invasion and local recurrence after curative surgical resection, as well as distant metastases. The growth rate and the presence of atypical cells are more critical for estimating the malignant potential of this type of tumor rather than size alone. Early diagnosis of HEAML plays a fundamental role in treatment, which may be challenging due to its atypical characteristics. We herein report the case of an atypical HEAML and conduct a systematic review of the relevant literature.

Case report

A 43-year-old Caucasian male patient visited his general practitioner due to a productive cough persisting for >2 months. Chest X-ray and laboratory tests revealed no specific pathological signs, and the physician suggested a chest computed tomography (CT) scan for further evaluation, which revealed multiple chronic obstructive pulmonary lesions and an incidental liver lesion. More specifically, the CT scan revealed a well-demarcated lesion, 7 cm in maximum diameter, located in the caudate lobe. The lesion exhibited heterogeneous enhancement following intravenous contrast administration and appeared to compress the intrahepatic portion of the inferior vena cava, without invading it. An abdominal magnetic resonance imaging (MRI) scan confirmed the findings of the CT (Fig. 1A-C). The hepatic lesion exhibited regular borders

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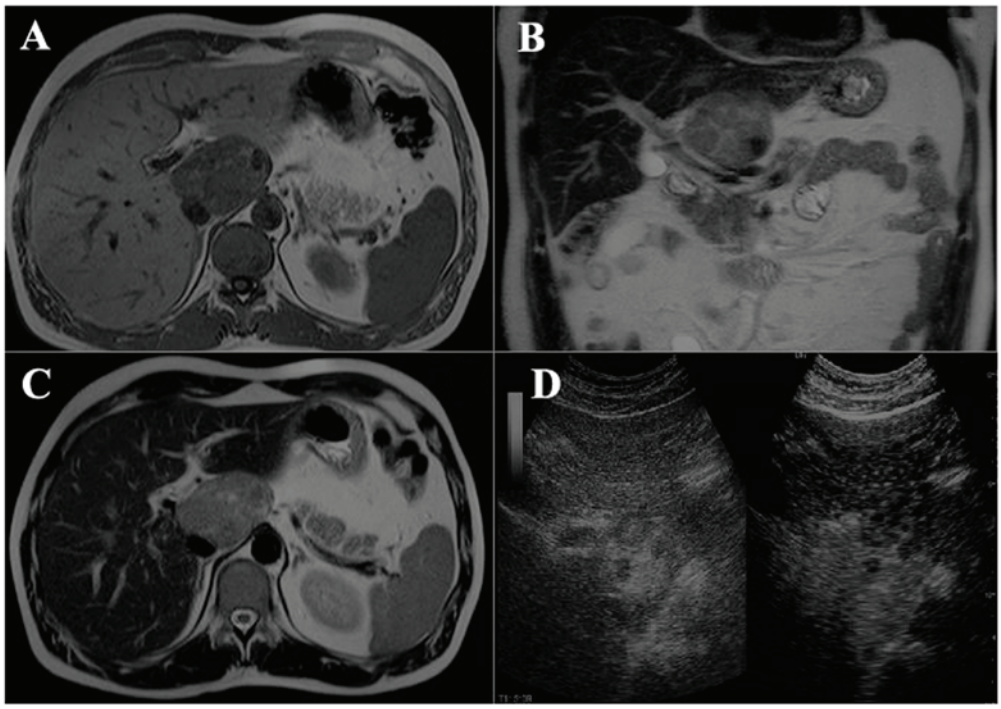

Figure 1. Imaging studies. (A-C) Magnetic resonance imaging of the hepaticlesion. (D) Contrast-enhanced ultrasound of the liver.

with areas of fatty tissue, and demonstrated early washout of the intravenous contrast medium and low attenuation in the portal phase. The possibility of hepatocellular carcinoma (HCC) at that time could not be excluded. Due to inconclusive cross-sectional imaging, a contrast-enhanced ultrasound examination was performed and revealed a hemodynamic behavior mimicking focal nodular hyperplasia (Fig. 1D). Physical examination revealed no abnormalities. Laboratory studies, including α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels, were within the normal range; the hepatitis virus markers were all negative.

Due to the inability of imaging studies to identify the true nature of the lesion and, more importantly, exclude malignancy, curative resection was performed. The patient underwent left hepatectomy with additional resection of segment I. The postoperative course was uneventful and the patient was discharged on the 7th postoperative day.

The tumor mainly consisted of two morphologically distinct components. The first component consisted of an admixture of adipocytes, abnormal blood vessels, perivascular epithelioid cells and sheets of foamy cells. These findings were considered to be foci of typical (classical) AML. In abrupt transition with this element, a second component with different morphology was identified. In particular, some tumor areas were composed of sheets of medium- to large-sized cells with epithelioid morphology. In addition, the cells exhibited vesicular nuclei with prominent nucleoli and eosinophilic cytoplasm (epithelioid AML). Focally, cells with bizarre nuclei, multinucleated forms and giant cells were identified. Mitoses were extremely rare. Tumor necrosis or vessel invasion were not detected. Furthermore, areas with cells with 'clear' morphology were identified. The latter areas were diagnosed as 'clear-cell' AML.

Immunohistochemically, the neoplastic cells expressed melanocytic markers, such as melan-A (Dako; Agilent Technologies, Inc., Santa Clara, CA, USA, clone A103, 1:150) and human melanoma black (HMB)-45 (Dako, clone HMB45, 1:150), while HepPar-1 (Dako; Agilent Technologies, Inc., clone OCH1E5, 1:20), S-100 (Thermo Fisher Scientific Inc., Waltham, MA, USA, clone 4C4.9, 1:800) and c-Kit (Dako; Agilent Technologies, Inc., rabbit, 1:600) were negative. The marker of cellular proliferation Ki-67 (Dako; Agilent Technologies, Inc, clone MIB-1, 1:100) was positive in ~5% of neoplastic cells.

The atypical histological characteristics in the present case included focal cellular pleomorphism, cellular atypia and large tumor size (>5 cm). The morphological and immunohistochemical findings were consistent with HEAML, including an element of 'typical' AML. No adjuvant treatment was administered postoperatively. The follow-up of the patient included medical history and physical examination every 3 months for the first year initially and every 6 months afterwards, along with abdominal MRI scan at 3, 6, 12 and 24 months. The patient remained asymptomatic and disease-free 2 years following the operation.

Discussion

In 2002, the World Health Organization recognized PEComas as a different entity, including neoplasms with perivascular epithelioid differentiation. PEComas include AMLs, lymphangioleiomyomatosis and clear-cell 'sugar' tumors (7). EAML is a type of AML composed almost exclusively of epithelioid cells, abnormal blood vessels and few or no adipocytes (8). The clinical characteristics of this type of tumor are usually silent, whereas their natural history has not yet been elucidated. The majority of reported cases

Table I. Patient characteristics.

Authors, year	Sex/age (years)	Epithelioid type	Location	Type of surgery	Metastasis	Re-op (yes/no)	Death (months)	RFS (months)	(Refs.)
Liu *et al*, 2016	M/34	Yes	Left lobe	Left lobectomy	NA	NA	NA	NA	(5)
Liu *et al*, 2016	F/31	Yes	Right lobe	Right lobectomy	NA	NA	NA	NA	(5)
Dalle *et al*	F/70	Yes	Right lobe	Right trisegmenectomy	Yes (liver)	No	NA	AW	(6)
Mizuguchi *et al*, 2004	F/49	Yes	Right lobe	Extended right trisegmentectomy	NA	NA	NA	NA	(26)
Flemming *et al*, 2000	F/51	Yes	Left lobe	Left lobectomy	No	Yes	No	36	(27)
Rouquie *et al*, 2006	F/67	Yes	Left lobe	Left lobectomy	NA	NA	NA	NA	(28)
Kamimura *et al*, 2010	M/52	Yes	S3-S4	Left lobectomy	No	No	No	AW	(29)
Fukuda *et al*, 2016	M/58	Yes	S5	Anterior segmentectomy	Yes (lungs)	Yes	No	36	(30)
Deng *et al*, 2008	M/30	Yes	Right lobe	Right lobectomy	Yes (pancreas and lungs)	No	Yes (42)	AW	(31)
Parfitt *et al*, 2006	F/60	Yes	Right lobe	Right lobectomy	Yes (trapezius muscle, liver, lung, pancreas)	Yes	No	108	(32)
Hu *et al*, 2011	NA/NA	NA	NA	NA	Yes	No	Yes (14)	AW	(33)
Kobayashi *et al*, 2013	F/46	No	Right lobe	Right lobectomy	NA	No	No	5	(34)
Yang *et al*, 2007	F/37	NA	Left lobe	Extended left lobectomy	No	No	Yes (9)	6	(35)
Nguyen *et al*, 2008	F/43	No	Left lobe	Left lobectomy and caudate lobe resection	Yes (peritoneum, gastrohepaticomentum, retroperitoneal space)	Yes	Yes (8)	6	(36)
Croquet *et al*, 2000	NA/NA	NA	NA	NA	NA	NA	NA	72	(37)
Ding *et al*, 2011	F/31	NA	Right lobe	Right lobectomy	No	No	Yes (7)	72	(38)
Wang *et al*, 2015	F/37	No	Left lobe	Left lobectomy	Yes (liver)	Yes	NA	NA	(39)
Xu *et al*, 2009	F/NA	NA	Left lobe	Left lobectomy	Yes	NA	NA	NA	(40)
Xu *et al*, 2009	NA/NA	NA	NA	NA	Yes	NA	NA	NA	(40)

F, female; M, male; NA, information not available; RFS, recurrence-free survival; AW, alive and well.

are incidentally discovered during routine check-ups or while conducting imaging examinations for other conditions. According to previous studies, the majority of the patients are asymptomatic, whereas patients with hepatic AML (HAML) may complain of abdominal discomfort (9-12). Tuberous sclerosis is associated with over half of the cases of renal AML and 5-15% of the cases of HAML (13). The majority of the patients have no history of liver disease or abnormalities in laboratory tests, and the tumor serum markers, including CEA, AFP and carbohydrate antigen 19-9, are usually within the normal range.

HAML is a heterogeneous tumor, which makes its distinction from various liver neoplasms based on imaging challenging, despite the advanced techniques currently available. Most HAMLs are misdiagnosed as malignant or focal liver lesions. Accurate diagnosis based on imaging studies alone is rare. On ultrasonography, HAMLs appear as heterogeneously hyperechoic masses. CT and MRI have similar

diagnostic accuracy rates, and both have a higher diagnostic accuracy compared with ultrasound (14). The presence of fatty areas and solid tissue components is a common presentation of HAML on CT or MRI. However, the presence of adipose tissue is unreliable, since HCCs may also contain fat (9). Other useful imaging characteristics on CT or MRI discriminating between HAML and HCC are the presence of early draining during the portal venous phase, a peripheral rim of decreased enhancement and the absence of a tumor capsule in the hypervascular hepatic tumor (9,15). The CT findings of HEAML, however, are related to the absence of adipose tissue in the lesions. In addition, recognizing imaging characteristics such as lack of a tumor capsule and hypervascularity, with central punctiform or filiform vessels as a characteristic enhancement may help distinguish HEAML from other hepatic tumors (16); however, only 25-52% of preoperative diagnoses are correct (17,18). Thus, despite the advances in imaging studies, histological diagnosis is necessary for treatment planning.

Differential diagnosis includes high-grade HCC, cholangiocarcinoma and rare sarcomas, such as epithelioid leiomyosarcoma of the liver. The morphological and immunohistochemical findings are usually sufficient for distinguishing these entities. HCC may display clear-cell changes, but immunohistochemically is positive for hepatocyte antigen. Cholangiocarcinoma is an adenocarcinoma and is characterized by the presence of atypical glands and glandular elements. Such neoplastic formations were not found in the present case. Epithelioid leiomyosarcoma may display clear-cell changes, but the tumor cells are negative for melanocytic markers. In the present case, malignant melanoma was excluded due to the lack of S-100 expression. Finally, gastrointestinal stromal tumors usually express the c-Kit marker, which was not observed in our case. Furthermore, the identification of the well-differentiated component of (typical) AML, strongly favors the diagnosis of EAML (19-21).

Atypical characteristics of EAML include a variety of macroscopic and histological findings, such as the size of the tumor (>5 cm), high mitotic rate, presence of atypical mitotic figures, vascular invasion, necrosis and cellular pleomorphism (2,7,22,23). In the present case, the large size of the tumor, cellular pleomorphism and atypical cells were evident, supporting the diagnosis of 'atypical' EAML.

The majority of HAMLs are considered to be benign, although several cases exhibiting malignant behavior have been reported, including tumor growth, presence of atypical cells, recurrence after surgical resection, metastasis and invasive growth into the liver parenchyma and alongside the vessels (24). Malignant transformation is considered to occur mostly in the epithelioid type (25). The first malignant AML was reported in 2000 by Dalle *et al* (6). The exact prevalence of malignant AML remains unknown. Most studies state that there have been ~6 cases of malignant AML reported in the literature to date. To the best of our knowledge, there have been 19 reported cases of malignant AML that are included in this review (5,6,26-40). Since the first case reported by Dalle *et al* (6), 18 more cases were reported thereafter. As summarized in Table I, 10 of those cases were HEAMLs, and only 3 were typical AMLs. The remaining 6 reported cases of malignant AML do not include an exact description of their cellular components. The recurrence-free survival in those cases ranges from 5 to 108 months. All patients with HEAML underwent surgery. The median age of this population was ~37 years. The majority of the patients with malignant HEAML were female (6/10). In 6 of the patients with malignant HEAML the mass was located in the right hepatic lobe and in the remaining cases it was in the left hepatic lobe.

A systematic review by Klompenhouwer *et al* suggested that, when the diagnosis of HAML based on imaging is certain, conservative management is recommended (3). The first surveillance imaging according to this review may be performed 1 year after diagnosis, with biennial follow-up thereafter. However, when the diagnosis is uncertain, biopsy must be performed. If biopsy is inconclusive or shows epithelioid characteristics, resection is indicated. Thus, the presence of epithelioid characteristics in AML is an additional indication for resection.

Although HAMLs were previously considered to be benign, surgeons should be aware of their malignant potential. When the diagnosis is uncertain or when epithelioid or atypical characteristics are found on preoperative biopsy, resection is indicated due to the high probability of malignancy; an aggressive approach contributes to diagnostic accuracy and definitive cure in cases of malignancy.

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Availability of data and materials

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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Authors' contributions

ZG, NM, IDK and PT made substantial contributions to data collection; histopathological analysis and the collection of images were conducted by AL and GL. Literature searching was performed by ZG and PT. ZG, NM, IDK and GCS drafted the manuscript; GCS reviewed the manuscript for intellectually important content. All the authors have read and approved the final version of this manuscript.

Competing interests

The authors declare that they have no competing interests to disclose.

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