

## Utility of Immunohistochemistry in the Diagnosis of a Case of Hepatic Angiomyolipoma from a Tertiary Referral Centre for Liver Diseases

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### Abstract

A single case of hepatic Angiomyolipoma (AML) over 25 years in a tertiary referral center for liver diseases is being presented. A 56-year old gentleman presented with abdominal pain, fullness and weight loss. A large left lobe mass in a background of non-cirrhotic liver was radiologically inscribed. The risk of rupture of together with the possibility of malignancy seedlings were the restraints against CT guided liver biopsy. Left lateral segmentectomy was the consulting surgical team's decisive maneuver. Gross pathological examination, histological evaluation and immunohistochemical analysis were performed to determine the nature of tumor. Results revealed normal serum levels of alpha-fetoprotein, CA 19.9 and carcinoembryonic antigen. Grossly the tumor exhibited variable consistency. Histologically, the tumor displayed three main constituents intermingled together; blood vessels, myoid cells and fat. Immunohistochemistry revealed positive immune reaction for CD34, alpha smooth muscle actin and S-100 in tumor tissue but negative for anti-human hepatocyte antibody.

**Keywords:** Mesenchymal tumor; Angiomyolipoma; immunohistochemistry

### Clinical History

A 56-year old gentleman presented to the Hepatology Clinic National Liver Institute, a tertiary referral center for liver diseases in Egypt, suffering from dull aching abdominal pain, fullness sensation, loss of appetite and weight loss. Pain persisted all the time, aggravated by meals mitigated by analgesics. Hepatomegaly with huge firm to hard left lobe mass were the only clinical data quoted from examination.

### Materials and Methods

Serological assays for hepatitis B, and C, were performed by ELISA and polymerase chain reaction (PCR). Alpha-fetoprotein, CA 19.9 and carcinoembryonic antigen (CEA) were measured in serum. Abdominal ultrasound, triphasic abdominal computed tomography and enhanced CT were done. The risk of rupture of this large sized lesion together with the possibility of malignancy seedlings were the restraints against CT guided liver biopsy. Accordingly, the decision of open surgery was the conclusive one. The patient was subjected to routine laboratory tests for surgical intervention. Left lateral segmentectomy of segments

II & III were performed and surgical specimens were sent to pathology department. The tumor mass was evaluated grossly, histologically and by immunohistochemistry. Immunohistochemistry was applied on tumor sections using CD34 antibody (Clone QBEND-10, ab8536, Abcam, Kemet, Egypt), anti-alpha smooth muscle actin antibody (ab5694, Abcam, Kemet, Egypt), anti S100 antibody (ab15520, Abcam, Kemet, Egypt) and anti-human hepatocyte antibody (Clone OCH1E5, Dako, Life trade, Egypt).

### Results

Laboratory data are shown in Table 1. Serological assays for hepatitis B, and C, were negative (HBsAg, anti-HBc-IgG, anti-HBc-IgM, anti-HCV-antibody), with a negative PCR for HCV. Serum alpha-fetoprotein, CA 19.9 and carcinoembryonic antigen were within normal ranges. Abdominal ultrasound revealed hepatomegaly with hypoechoic left lobe mass 5.5 × 4.1 cm, regular in shape with clear borders. In enhanced CT, the arterial phase was non homogeneously strengthened. The enhancement was weakened during the portal venous phase and delayed phase but still heterogeneous in nature adding more ambiguity to this dilemma. Most of case reports of HAML published in literature was demonstrated in Table 2 with all their demographic criteria [1-19].

	Admission results	Discharge results
Total bilirubin mg/dL	1.2	0.9
Direct bilirubin mg/dL	0.6	0.5
Albumin g/dL	3.8	4.3

AST U/L	34	23
ALT U/L	39	37
ALP U/L	273	88
GGT U/L	122	45
INR	1.04	1.04
HG g/dL	13.7	14
WBCs/10 <sup>3</sup>	7.2	6.1
Platelets/10 <sup>3</sup>	190	234

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, PC: Prothrombin concentration, INR: international normalized ratio, HG: haemoglobin, WBCs: white blood cells, NAD: no abnormality detected.

**Table 1:** Laboratory data of the case.

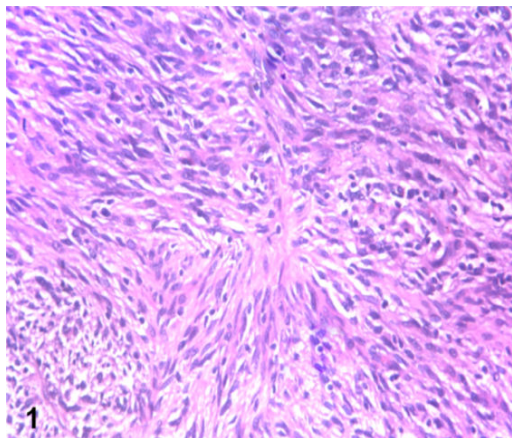
Author	N of cases	gender	age	site	Main clinical presentation	Outcome
Sing et al. [1]	1	F	54	R	Fatigue+ abdominal pain	Surgical removal with fruitful outcome
Gungor et al. [2]	1	F	57	R,L	Back pain	Surgical removal with fruitful outcome
Aiyappan et al. [3]	1	F	52	L	Accidentally discovered	Partial hepatectomy
Jyothi et al. [4]	1	M	50	L	Abdominal pain Fever	Segmentectomy
Yang et al. [5]	1	M	58	R	Accidentally	Segmentectomy and death related lung recurrence after 7 years
Nonomura et al. [6]	47	36% F	54	15 L 11 R 21 R,L	36% accidental	Only one case died from pneuminia
Taliata et al. [7]	1	M	50	L	Abdominal pain Fever	Segmentectomy
Romano et al. [8]	1	F		R	Accidental	Surgical removal
Tsui et al. [9]	30	F to M 25:5	48	R,L	Heaviness, accidental and rupture tumour	Surgical removal
Shi et al. [10]	5	0.167361	39	2 L 3 R	Accidental	Surgical removal with no recurrence
Kojima et al. [11]	1	F	21	L	Accidental	Surgical removal with no recurrence
Agaimay and Markl [12]	1	F	51	L	Constitutional symptoms	Surgical removal with no recurrence
Kai et al. [13]	1	F	77	L	Rupture tumor	Surgical removal with no recurrence
Nonomura et al. [14]	50				Abdominal pain	Surgical removal with no recurrence
Kim et al. [15]	1	M	32	R	Abdominal pain	Surgical removal with no recurrence
Montoriol et al. [16]	1	F	25	R	Abdominal pain	Liver transplantation
Ren et al. [17]	26	F:M 0.878472	55	R, L	Accidental	Surgical removal with no recurrence
Takahara et al. [18]	1	M	56	L	Abdominal heaviness	Surgical removal with no recurrence
Maebayashi et al. [19]	1	M	58		Abdominal bloating	Surgical removal with no recurrence

F: Female; M: Male, R: Right; L: Left; N: Number

**Table 2:** Angiomyolipoma registered case reports.

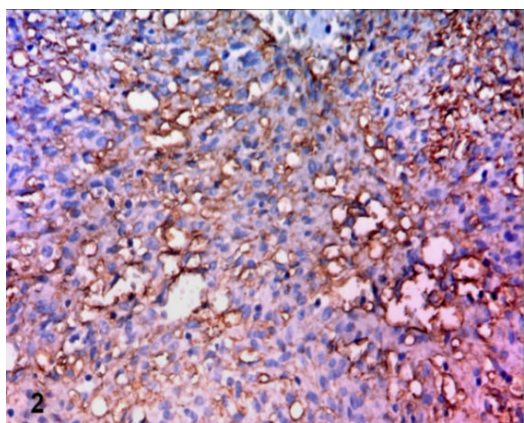
**Pathological findings:** Gross examination revealed a huge well circumscribed not encapsulated nodular mass 22.0 cm largest diameter. The tumor varied in consistency displaying soft and firm components. Histological examination of the mass revealed variable

patterns included: tortuous vessels, myoid cells and fat. Tortuous, thick walled vessels were often rimmed by epithelioid myoid cells but a sinusoidal pattern was not present. Myoid cells varied between epithelioid, spindled or intermediate. Spindled myoid cell typically had pale or clear cytoplasm and were arranged in fascicles (Figure 1).

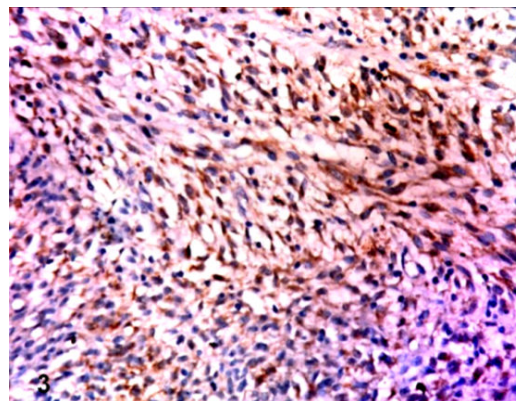


**Figure 1:** Spindled myoid cells.

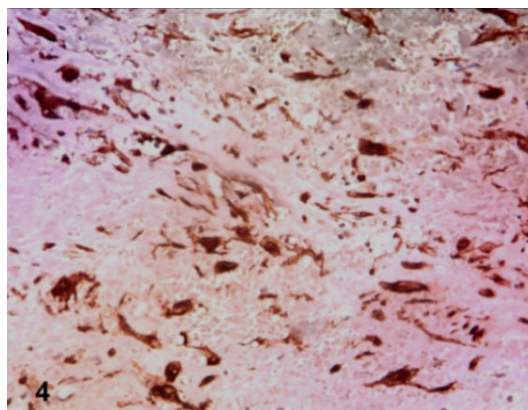
More cellular areas within the tumor had a hepatoid look with more crowded nuclei and less cytoplasm. A very small amount of fat was noted within the tumor that was typically mature, however, lipoblast like cells were occasionally found. Within the tumor nodule there was an entrapped portal tract. Liver away from the tumor showed nonspecific pathological changes with no cirrhosis. Immunostaining results revealed CD34 antibody immunoreactive to endothelial cells lining blood vessels (Figure 2), alpha smooth muscle actin antibody immunoreactive to spindle myoid cells (Figure 3), S100 antibody immunoreactive to fat cells (Figure 4), while anti human hepatocyte antibody was found to be negative in tumor cells, immunoreactive to hepatocytes away from the tumor (Figure 5).



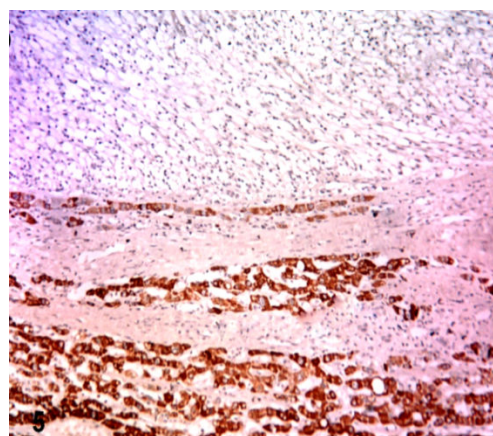
**Figure 2:** Positive immunostaining of CD34.



**Figure 3:** Positive immunostaining of SMA.



**Figure 4:** Positive immunostaining of S-100.



**Figure 5:** Negative immunostaining of AHH, positive outside the tumor.

Histopathology report was titled with confidence: Hepatic angiomyolipoma. The patient was followed up postoperatively for one week then discharged. The patient kept on monthly visits for one year



with completely normal profiles. Consequently, yearly visits were scheduled with normal studies for three years till now.

## Discussion

AML is more frequently found in the kidney [20]. The first case of HAML was reported by Ishak et al. in 1976 [21]. In spite of the fact that HAML is mostly reported in females [5,9], no relation was ascertained to either estrogens, androgens or their receptors or their receptors has been suggested [22].

Clinically HAML cases always Clinically HAML cases always are symptomless. Consequently, in most instances, incidental discovery was the main presentation [6]. Dull abdominal, and back aches, along with fever, fatigue was also reported [1,12,16]. However two case reports had registered aneurysmal rupture, and Budd-Chiari syndrome caused by compression of hepatic vein [23,24]. Dull upper abdominal aches, loss of appetite attributed to our case might be due to the large size of the tumor with compressing symptoms. HAML had been frequently ascribed preferably in the left lobe of the liver [1]. Actually; the diagnosis of hepatic AML is not easy. A collaboration of imaging techniques and hepatic leisional biopsy, are the most recommended for proper HAML diagnosis. The radiological features of hepatic AML vary according to its histological components [9]. Hepatic AMLs on radiologic examination may mimic HCC especially those with fatty change; are difficult to differentiate from AML [25]. The histogenesis of AML is unclear. The unique nature of its triple cellular components had made preoperative perception of HAML, with indisputable preoperative diagnosis -in its best conditions- only up to 53% [26]. The rapid growth and malignant potency, along with the concomitant misdiagnosis with hepatocellular carcinoma; had substantially vindicated surgical intervention [27,28]. Recurrence was infrequent consequence following segmentectomy. However, recurrence related death had been encountered in a case of malignant HAML with late recurrence in the lung after hepatectomy [5] (Table 2). Studies have demonstrated evidence suggesting a clonal proliferation that favors a neoplastic process. Some authors believe that various cell types are derived from precursor cells present in the perivascular space [29]. Perivascular epithelioid cells (PECs) are thought to be more primitive cells that differentiate to become spindled myoid cells or fat cells [30]. These PEC cells have no normal corollary and are thought to be the precursor of a group of lesions that can be found in many different organs [30]. In 2002, the classification of soft tissue tumors released by the World Health Organization; HAML was classified as perivascular epithelioid cell tumors (PEComas) [31].

The primary differential diagnosis of HAML is with hepatocellular carcinoma, lipoma, leiomyosarcoma, haemangioma and epithelioid leiomyosarcoma. Other tumours abounding with blood vessels, such as haemangioma, focal nodular hyperplasia, or hepatic adenoma, with approaching imaging features, are also difficult in discrimination [32]. Owing to the multiform histological variations of the three components of HAML; the conventional imaging examinations such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) shows indistinctive imaging characteristics [33]. In ultrasound the echogenicity of the tumor relied mainly upon the most predominant of the three cellular components [34]. In our case intraoperative histological examination of the resected tumor seem to be not malignant and not HCC. In addition to the microscopic morphology, immunohistochemistry staining was used to improve the diagnostic specificity for HAML. S-100, a specific antibody against human melanocytic tumor, it only reacts with HAML besides

hepatoblastoma in liver tissue. Together with the expression of CD34, smooth muscle actin (SMA), and CD117, these markers play significant roles in the diagnosis of HAML. CD34, SMA, and S-100 were the immunohistochemical verifying tread. The nil reaction to anti human hepatocyte antibody is the substantial evidence of absence of hepatocytes in tumor cells.

To sum up, HAML diagnosis can be puzzled out only by gathered efforts of a multidisciplinary medical team formed of clinicians, radiologists, surgeons and pathologists; in order not to miss even a single case.

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