

ORIGINAL PAPERS

## Epithelioid angiomyolipoma of the liver: Clinicopathological correlation in a series of 4 cases

Santiago Ortiz and Francisco Tortosa

*Department of Pathology, Centro Hospitalar Lisboa Norte, EPE - Hospital de Santa Maria, Lisbon, Portugal*

### ABSTRACT

Hepatic angiomyolipoma is a rare neoplasm that can be difficult to diagnose in cases of ecoguide biopsy. We studied 4 cases of female patients with a mean age of 51 years. None of the patients presented specific abdominal symptoms, or other tumour masses detected by chance. One of them had relevant personal history: Renal cell carcinoma. This same patient was diagnosed with a contralateral renal angiomyolipoma. None of the patients showed evidence of tuberosus sclerosis. Three tumours have been diagnosed by biopsy and only in one patient was decided to completely remove the tumour surgically. None of the patients had evidence of recurrence of disease or an increase in tumour size over an average period of 45 months. Histologically, the tumours have been sub classified into angiomyolipomas epithelioid. In 50% of the cases, extramedullary haematopoiesis was observed. The first diagnostic impression using imaging methods included: Focal nodular hyperplasia, hepatocellular adenoma, hepatocellular carcinoma and metastasis. By immunohistochemistry, it has been demonstrated that all tumours expressing melanocytic markers (HMB45 and Melan A) and markers of smooth muscle cells (smooth muscle actin). The diagnosis of these tumours is increasing due to programmes for early detection of hepatocellular carcinoma in patients with liver cirrhosis. It must be taken into account their broad spectrum of morphological diversity to avoid incorrect diagnosis of a malignant neoplasm.

**Key words:** Angiomyolipoma. Liver. PEComa.

### INTRODUCTION

Benign tumours lesions of the liver may have its origin in hepatocytes (focal nodular hyperplasia, nodular regenerative hyperplasia, hepatocellular adenoma), in mesenchymal cells (haemangioma, fibrous tumour, smooth muscle tumours...) or can be mixed (angiomyolipoma).

Perivascular epithelioid cell neoplasms of -PEComas have been first described by Bonetti et al. in 1992. Ten years later, in 2002, PEComas have been recognized as an

independent entity according to the World Health Organization (1).

The family of PEComas include: Angiomyolipoma of the kidney and extra renal, clear cell sugar tumour of the lung and extra pulmonary, lymphangioliomyomatosis, clear cell myomelanocytic tumour of the falciform ligament and PEComa not otherwise specified, which appears intraparenchymal and in the soft tissue lesions (2).

Angiomyolipomas are rare neoplasms of mesenchymal origin, derived from perivascular epithelioid cells. In the liver it is a very infrequent benign neof ormation. It is much more frequent in kidney presentation, as it appears in 0.3% of the population and represents 3% of the renal masses (3).

PEComas are very rare tumours in other anatomical locations that are not kidney and lung; however cases have been described in colon, pancreas, retroperitoneum, heart, adrenal gland, breast, eye, biliary tree, bone, urinary bladder, skull base, uterine cervix, skin, nasopharynx, and liver (4).

Currently the diagnosis of these tumours are increasing, but not by the growth of the prevalence of the tumour, if it was not for the programmes of early detection of hepatocellular carcinoma in patients with liver cirrhosis. Also due to the widespread development and use of imaging studies, implying that every time hepatic asymptomatic benign lesions are frequently diagnosed (5).

Nevertheless, hepatic angiomyolipoma is a difficult diagnostic entity by both, clinicians and pathologists. Typical lesions such as haemangioma or focal nodular hyperplasia are already well known and they are widely documented in literature, allowing a diagnosis with some certainty. However the uncommon lesions are, as a rule, a diagnostic challenge.

Most of the hepatic angiomyolipomas have been misinterpreted as hepatocellular carcinoma by imaging methods (6). Diagnosis of these tumours depends predominantly on the immunohistochemical study and on the expression of melanocytic and smooth muscle markers.

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Correspondence: Santiago Ortiz, Department of Pathology, Centro Hospitalar Lisboa Norte, EPE - Hospital de Santa Maria, Av. Prof. Egas Moniz, 1649-035, Lisbon, Portugal  
e-mail: santi.orfer@gmail.com

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The aim of this paper is to present our cases and give an update in relation to the diagnosis, illustrating their heterogeneity and immunohistochemistry profile in the diagnosis by ultrasound core needle biopsy and surgical resection specimen, in the Centro Hospitalar Lisboa Norte, the largest reference centre in Portugal.

## PATIENTS AND METHODS

For the elaboration of the present study, a search has been carried out of all cases of hepatic angiomyolipoma diagnosed in the Pathology Department of the Centro Hospitalar Lisboa Norte, between 01/01/2000 and 31/12/2014. The follow-up of the patients was made by studying the clinical processes.

All the liver tissue samples that are received in our department follow this procedure: They are fixed in 10% buffered formaldehyde for at least 8 hours and up to 24 hours; after being fixed for this period of time they are mounted in paraffin wax; later, using a microtome, sections of these paraffin blocks were cut with a 2 µm thickness to haematoxylin and eosin stain, 4 µm sections to histochemistry stains (CAB, PAS with diastase predigestion, Sweet and Perls) and 2 µm sections to immunohistochemistry studies where the following individual antibodies have been used: Smooth muscle actin (clone - 1A4, dilution 1:150, source - Dako), HMB45 (clone - HMB45, dilution - 1:150, source - Cell Marque), Melan A (clone - MART-1, pre-diluted, source - Ventana, Roche). Morphologic features and immunohistochemically profile for the diagnosis of hepatic angiomyolipoma are based on the 2010 version of the World Health Organization on liver tumours (7).

Conducting a review of the medical literature, we have found more than 300 cases since the first description of hepatic angiomyolipoma by Ishak in 1976 (3). This review was carried out in May 2015, using PubMed and MEDLINE searches for articles on hepatic angiomyolipomas. Our keywords include: Angiomyolipoma, epithelioid, hepatic and diagnosis. We have studied the case reports and review articles, excluding experimental and veterinary works. In addition, we critically reviewed the reference lists of the articles that we found. The language of this search was restricted to English and Spanish, and the time period to after 1976.

## RESULTS

The clinicopathological features are summarized in table I. Four hepatic angiomyolipomas have been diag-

nosed in the last 15 years in our centre, all in female patients. The age range was between 41 and 60 years, with an average of  $51 \pm 9.8$  years.

The dimensions of the hepatic nodules range between 1 and 7.5 cm in the greatest shaft.

None of the patients presented specific abdominal symptoms, or other tumour masses detected incidentally. In only one patient was decided to completely remove the tumour surgically and on the other three ultrasound-guided biopsies only have been performed and followed-up by monitoring imaging techniques. Evidence of recurrent disease, increased tumour size or appearance of new tumours in other locations, has not been observed in these three patients, during a follow-up period that ranged between 24 and 60 months (average, 45 months). One of the patients diagnosed by biopsy subsequently was detected with a renal angiomyolipoma. Previously, this same patient had already been diagnosed with a renal cell carcinoma in the contralateral kidney, with pulmonary metastasis. He has also undergone surgery for a papillary carcinoma of the thyroid gland. Today all patients are alive and none have other hepatic neoplasia. None of the patients have been known to suffer from tuberous sclerosis.

Using different imaging methods, the characteristics of the nodules have been interpreted as: Focal nodular hyperplasia/adenoma, hepatocellular adenoma, hepatocellular carcinoma and metastasis.

Histologically all tumours were diagnosed as hepatic epithelioid angiomyolipoma (PEComa). It is a compound tumour which combines mature adipose tissue with haphazardly distributed spindle to epithelioid muscle cells with clear vacuolated or eosinophilic granular cytoplasm and a variable number of thick walled vessels.

In the case of the surgical specimen, where different areas of the tumour were studied (unlike biopsies), we found areas with inflammatory infiltrate among spindle-cell stroma, which would suggest the differential diagnosis of inflammatory pseudotumour; focally oncocyctic myoid cells with abundant eosinophilic granular cytoplasm, resembling hepatocellular carcinoma; also in this case, this neoplasm can be mistaken for liposarcoma owing to the presence of lipoblast-like cells, with multiple cytoplasmic vacuoles. Immunohistochemically, the

**Table I. Clinical and radiological features of hepatic angiomyolipoma**

Sex; age (years)	F 60	F 41	F 55	F 48
Symptoms	Non-specific	Abdominal pain	Follow up for renal cell carcinoma	Incidental
Clinic/radiological diagnosis	Hepatocellular carcinoma / metastasis	Focal nodular hyperplasia / adenoma	Metastasis	Adenoma
Tumour size (cm)	2	7.5	1	6
Intervention	Core needle biopsy	Core needle biopsy	Core needle biopsy	Surgery

F: Female.

tumour cells are positive for HMB45, Melan A and smooth muscle actin (Fig. 1).

## DISCUSSION

Hepatic angiomyolipoma is an extremely rare lesion that until 1984 only 14 cases were reported in the English literature.

The age of presentation is between the 30 and 65 years of age, although cases have been reported in patients as young as 16 years old. It has a clear female predominance, ratio 4:1 (3). Our cases have a very typical presentation as all our patients are female, with ages in the range described in the literature.

About 40-50% of the patients with renal angiomyolipomas suffer from tuberous sclerosis. At hepatic level, only 10% of the patients suffer concomitantly with tuberous sclerosis (8), so hepatic angiomyolipoma may appear in the context of a tuberous sclerosis or on its own. Associated with tuberous sclerosis there is a finding that we have not objectified in our series.

From a clinical point of view, angiomyolipomas are usually asymptomatic, although they may cause nonspecific abdominal pain, associated with tumour size. Half of the cases are accidentally detected by imaging methods. Using these techniques (ultrasound, computed tomography and magnetic resonance) hepatic angiomyolipomas are presented as rounded shape, well defined and isolated lesions. The preoperative diagnosis by imaging is very difficult and oscillates from 0 to 23%, being 11% for computed tomography and 23% for magnetic resonance

(6). From the radiological point of view there is no technique or specific image that is able to differentiate hepatic angiomyolipoma from another benign or even malignant tumour, hence most are diagnosed as haemangioma or hepatocellular carcinoma (6).

As imaging methods can mimic other tumours, the definitive diagnosis is always provided by pathological studies. Histologically these tumours are composed by aggregates and sheets of mature adipose tissue, tortuous thick-walled vessels and perivascular muscle cells proliferation. The epithelioid concept applies when one of the three components of these tumours, mainly smooth muscle cells, has rounded or polygonal appearance, with a large round nucleus, prominent nucleoli and abundant eosinophilic cytoplasm (oncocyctic). These perivascular epithelioid cells are one of the diagnostic clues.

The histopathological diagnosis is not easy, let alone by core needle biopsy. This is due to the fact that it's a tumour with a high heterogeneous appearance, which can mimic pseudotumoral lesions, primary or metastatic tumours (8,9).

The differential diagnosis must be individually assessed according to the predominant cell type and growth pattern of the lesion. The absence of cellular atypia and epithelioid cells with clear or granular cytoplasm in perivascular localization (pattern PEC), should make us think more about an angiomyolipoma. In case of doubt you should do an immunohistochemical study, being the cells of hepatocellular carcinoma positive for HepPar-1, CEA polyclonal and CD10 and angiomyolipoma's cells for HMB45, Melan A and smooth muscle actin.

The pathogenesis of hepatic angiomyolipoma is unknown, since the primordial cell of these tumours is of unknown origin. Possible progenitors that have been considered are the undifferentiated cells of neural crest, differentiated smooth muscle cells and pericytes (2).

In a recent study, Malinowska et al. demonstrated the TFE3 expression in PEComas of patients without associated tuberous sclerosis (10). Based on this study it can be said that rearrangement of TFE3 plays an important role in the pathogenesis of this tumour. Immunoreactivity for TFE3 has been observed in younger patients, which the tumour has epithelioid cytological features and have low expression for muscle markers (11).

Exceptionally angiomyolipomas may have a malignant behaviour. Considering the heterogeneous nature of the tumour, we cannot rule out malignancy completely. To establish a malignant potential of PEComas is challenging. Although the majority show a benign course, some are aggressive with local recurrence and distant metastasis (12-14).

To date, none of the three proposed systems to stratify the risk of malignancy have been accepted: Folpe et al. in 2005, Brimo et al. in 2010 y Bleeker et al. in 2012 (12-14).

Despite its benign nature, the difficulty to discard malignancy requires surgical treatment. The surgical resection is

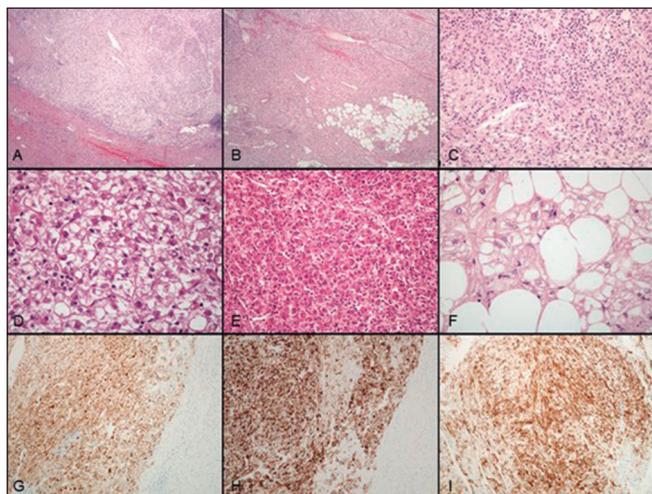


Fig. 1. Histologically the tumour consists of adipose tissue, thick-walled vessels and sheets of epithelioid muscle cells (A and B - H & E x40). There are inflammatory infiltrated areas (C - H & E x200), clear epithelioid cells (D - H & E x400), oncocyctic myoid cells (E - H & E x200) and presence of lipoblast-like cells (F - H & E x400). The cells show immunoreactivity for HMB45 (G - x100), Melan A (H - x100) and smooth muscle actin (I - x100).

the only potentially curative treatment of primary PEComas and to prevent local recurrence or metastasis (14).

Asymptomatic small tumours with biopsy histopathological diagnosis, may not require an operation however it is essential to perform a strict control of the neoplasm. Recommendations do not exist on how to follow up, but it is necessary to keep in mind that we don't know its way of growth, which could give compressive symptoms, and there is the possibility of rupture and malignant transformation. In cases which surgical resection is performed, recurrence is rare, although there is some cases described (15).

Epithelioid angiomyolipomas of liver diagnosed in our extensive archive of liver pathology are in accordance with those described in the literature. As far as we know, this is the first comprehensive and updated work performed in Portugal, also being the first series of liver PEComas in this country and one of the largest series of a single centre in Europe.

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