What do you know about liver PEComa? A case report

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Learning objectives

-To describe the imaging findings of liver PEComa in US, CT and MR with specific liver contrast agent (Gd-EOB-DTPA) and gadolinium

-To review the current literature about this rare neoplasm
Background

PEComa is a very rare mesenchymal neoplasm which is formed by distinctive perivascular epithelioid cells, characterized by dual melanocytic and myoid differentiation.

At first, to establish this cell type identity the hypothetical descriptive term perivascular epithelioid cell (PEC) was proposed. Despite some initial problems of acceptance, finally, the concept of PEC-tumors was approved by the World Health Organization.

Nowadays, perivascular epithelioid cell tumors are defined as a group of mesenchymal tumors that includes entities with distinct clinicopathological features and a factor in common, the perivascular epithelioid cell, which expresses myogenic and melanocytic immunohistochemical markers. This family includes angiomyolipoma (renal and extrarenal), clear cell "sugar" tumor of the lung, lymphangioleiomyomatosis and a number of unusual visceral, intra-abdominal, soft tissue, and bone tumors, which have been referred to by a variety of names including primary extrapulmonary sugar tumor, clear cell myomelanocytic tumor and abdominopelvic sarcoma of perivascular epithelioid cells, among others. This latter subset has been collectively termed perivascular epithelioid cell tumors-not otherwise specified (PEComas-NOS); or non-AML, non-LAM, non-CCST PEComas or PEComas other than AML, LAM, or CCST. Some authors have advocated the use of the term myomelanocytic tumor as a sensible designation for these tumors, although the term PEComa has become the popular umbrella term for this latter list of lesions.

Although AML, LAM, and pulmonary CCST are well described, relatively little is known about PEComa-NOS. They have been described in different organs and are considered ubiquitous tumors. There are reported cases in almost every body site, and the list of sites includes gastrointestinal (liver, falciform ligament/ligamentum teres, duodenum, ileum, jejenum, colon, rectum, abdominal serosa, common bile duct, pancreas), gynecologic (uterus, broad ligament, vulva), genitourinary (prostate, urinary bladder, kidney), extremities, pelvic wall, retroperitoneum and skin, as well as single reports in the heart, breast, oral cavity, orbit and skull base.

Up to 40% of these tumors arise in gynecologic locations, most commonly the uterus. The other common sites are the genitourinary tract, gastrointestinal tract and retroperitoneum, whereas rare sites include somatic soft tissue, skin and bone.

The primary PEComa of the liver is an extremely rare entity, and most of the reported cases are referred to as angiomyolipomas, either classic or epithelioid. Only a few cases
PEComa-NOS of the liver have been described worldwide so far. Because of its rarity, little is known about these lesions, followed by further difficulties in the establishment of the diagnosis.

This review examines the exceedingly rare liver PEComa-NOS subset of the PEComa family of tumor.

**EPIDEMIOLOGY**

These tumors can arise in patients of virtually any age, ranging from 15 to 70 years of age, although the peak incidence is in the fourth-fifth decade of life. There is a striking female predominance. They are usually solitary lesions localized predominantly in the right lobe.

The strong association between AML, LAM, CCST and tuberous sclerosis is well known, but this relation is much less clear for PEComas-NOS.

**CLINICAL FEATURES**

The clinical presentation of liver PEComa is not specific and symptoms and signs are similar to other tumors arising from the liver. Most of them are asymptomatic. The most common symptoms are abdominal pain, fever, bleeding, indigestion, loss of appetite, abdominal distension, weight loss and nausea; on physical examination tenderness to palpation and liver enlargement may be identified.

Therefore, usually, these lesions are incidentally diagnosed, thus the tumor size is highly wide, ranging between 1 and 36 cm.

Routine laboratory tests are noncontributory, because liver function tests are normal, hepatitis B surface antigen and hepatitis C virus antibody are negative and the serum #fetoprotein level and other tumoral markers remain within the normal range. Although there are reported cases of liver PEComas in hepatitis C virus positive patients, there have not been described a causal relation between them.

Imaging studies, as we describe below, have a limited value.

**PATHOLOGIC FINDINGS**
Gross Features

On gross examination, PEComas are generally circumscribed, although no definite capsule is present and some are histologically infiltrative into the surrounding tissue. The cut surface is white-tan to gray-red; it may be solid, firm or, even, myxoid, and areas of hemorrhage or necrosis may be appreciated.

Histological Features

The perivascular epithelioid cell has morphologic, immunohistochemical, ultrastructural and genetic distinctive features.

PEComas-NOS are usually biphasic tumors with epithelioid and spindle cell components. Great variation is seen in the relative proportion of both kinds of cells.

Histologically, these cells have clear to granular, lightly eosinophilic cytoplasm, and relatively uniform, small, centrally placed, round to oval nuclei with small nucleoli, slight atypia and sparse mitotic activity. PECs are arranged into nests, fascicles, and, occasionally, sheets, with a typical perivascular location, often with a radial arrangement around blood vessels. Overall cellularity is usually low to moderate, but some cases are highly cellular. The presence of multinucleated giant cells are common.

Most tumors have few, if any, mitotic figures, but some, especially those of higher nuclear grade, may have prominent mitotic activity, including atypical mitotic figures. Coagulative necrosis and angiolymphatic invasion are uncommonly identified.

At present, PEC has not a known normal cell counterpart.

Immunohistochemical Features

PEComas-NOS tipically show immunohistochemical evidence of both smooth muscle and melanocytic differentiation. Usually, they are strongly positive for melanocytic markers, such as HMB-45 (monoclonal antibody highly specific for melanocytes), Melan-A/MART-1, microphthalmia Transcription Factor (MiTF) and tyrosinase, and show variable expression of smooth muscle markers such as smooth muscle actin (SMA), muscle-specific actin/all-muscle actin/HHF-35, muscle myosin, desmin, caldesmon and calponin.
Desmin is less often positive, and cytokeratins and S100 protein are usually negative. Although uncommon, rare cells can express CD 117 (KIT).

Malignant PEComas-NOS tipically demonstrate a high proliferative index with Ki-67 immunostaining.

We recommend that all unusual carcinomas and mesenchymal tumors of the liver should be tested for HMB-45: when positive, there is a high likelihood of PEComa.

Depending on specific microenvironment locations, PECs can modulate their morphology and immunophenotype; in some conditions, PECs can pronounce muscle features with spindle shape and in other they can exhibit more epithelioid morphology with strong positivity for HMB45 and weak or focal expression for SMA. PEC can also become vacuolized acquiring the feature of an adipocyte.

**Electron Microscopic Features**

Ultrastructurally, the cells of PEComas are characterized by abundant cytoplasmic glycogen, the presence of premelanosomes, hemidesmosomes, thin filaments, and poor intracellular junctions.

**Cytogenetic and Molecular Features**

The cytogenetic features of PEComas-NOS have not been extensively studied to date.

AML, LAM AND CCST are related to the genetic alterations of tuberous sclerosis complex (TSC), a genetic disease due to losses of TSC1 (9q34) or TSC2 (16p13.3) genes. Similar alterations of the TSC genes have been demonstrated in a significant number of this subset of PEComas, both occurring within the TSC and in sporadic cases. However, TSC1 and TSC2 genes do not appear to be important in the pathogenesis of most PEComas-NOS. Recent studies suggest that the overexpression of cyclin D1 may play a role in the development of this tumors, although the results are not definitive.

**Differential Diagnosis**

From an immunohistochemical and cytogenetic point of view, the differential diagnosis of a liver PEComa, with myomelanotic differentiation, should include gastrointestinal
stromal tumors, metastatic clear cell carcinoma (lung, ovary, kidney), metastatic melanoma and metastatic clear cell sarcoma. The immunohistochemical findings play a crucial role in ruling out any misdiagnosis and mistreatment of these lesions.

**BIOLOGICAL BEHAVIOUR AND PROGNOSIS**

Most of the reported PEComas-NOS seem to behave in a benign fashion, although cases with local aggressive behaviour or recurrences, distant metastases or, even, patient death have also been described. A few malignant PEComas metastasized after several years (7-9 years).

A recent study suggested some histological features potentially related to malignancy, which have been defined as a high mitotic activity (> 1 MF/50 HPF), coagulative tumor necrosis, high nuclear grade, hypercellularity, infiltrative growth pattern and large tumor size (>5 cm).

Based on these criteria, a provisional classification of PEComas into benign, uncertain malignant potential and malignant categories has been proposed. *(Table 1 on page 9)*

PEComas with a Ki-67 labeling index of less than 1% have neither recurred nor metastasized. However, Ki-67 labeling of 5% of neoplastic cells has been observed in uterine PEComas that have behaved aggressively.

However, the definitive criteria of malignancy in PEComa have not yet been formally established. The biological behaviour is often unpredictable; there are cases in which metastases occurred, although malignant histological features of primary tumor were not confirmed, and other cases with metastatic spread presented after many years, as a late complication. Because of this, a long-term periodic follow-up is reasonable in every case.

**TREATMENT**

Optimal treatment for PEComas is not well established at this time. Currently, the gold standard for treatment of hepatic PEComa is the surgical resection with an adequate margin of healthy tissue, and it represents the only curative approach for primary PEComa at presentation as well as for local recurrences and metastasis. Since most PEComas are benign, this treatment is usually curative.
Metastases have been successfully managed by resection alone. Advanced disseminated neoplasms are associated with a poor prognosis, and other treatment modalities like radiotherapy, chemotherapy and interferon-# immunotherapy have been reported. The role of adjuvant therapy remains unclear.

However, no therapeutic trial has been implemented and this management derives from anecdotal reported cases; there are obvious difficulties to perform a therapeutic trial mainly due to the rarity of the disease.

The creation of an international PEComa clinical register is strongly necessary, to improve our general knowledge about the incidence, natural course, prognostic and risk factors, optimal treatment modalities and follow-up in this kind of tumor.
### Table 1: PROPOSED CLASSIFICATION OF PEComas

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Imaging findings OR Procedure details

Imaging studies can confirm the presence of the tumor, its location, size, inner structure and relations with other organs, since there are no definite imaging characteristics indicating PEComa. A well-defined preoperative diagnosis is hard to make because of non-specific radiological features. Preoperative biopsy might overcome this limitation, but the data coming from current clinical practices suggest that PEComa diagnosis is usually confirmed after surgery.

Usually, the patient study begins with an ULTRASOUND EXAMINATION, where PEComa appears as a focal solid mass, with well-defined margins and heterogeneous inner echostructure, although hyperechogenic areas are predominantly.

For an accurate diagnosis, an unenhanced and a multiphase COMPUTED TOMOGRAPHY must be carried out.

Plain CT shows PEComa as a homogeneous, low-attenuated and well-defined nodule. The presence of areas with negative attenuation values (-20 UH) within the tumor proves the existence of intratumoral fat, which is very suggestive of angiomyolipoma, but there are always not present and it is not typical of PEComas-NOS.

Next, an enhanced CT after intravenous injection of iodinated contrast medium with arterial, portal and delayed phases must be performed. On arterial phase, the lesion is hypervascular (hyperenhanced compared with the surrounding liver parenchyma), with wash-out of contrast medium on portal or delayed phases. Sometimes, PEComa can remain hyper- or isodense on these phases. Unlike the hepatocellular carcinoma, PEComa has not a peritumoral capsule.

In MAGNETIC RESONANCE IMAGING, this lesion is visualized as a hypointense nodule on T1-weighted images and a hyperintense nodule on T2-weighted images. Hyperintense areas in T1-weighted MRI suggest the presence of intratumoral fat, what can be demonstrated using fat-suppression and chemical shift sequences. In dynamic sequences, the behaviour is similar to the CT one.

It is very difficult to decide the best imaging technique for the diagnosis of PEComa-NOS, because there are not patognomic findings in any of them. Contrast enhancement pattern of PEComa is similar to the pattern described in malignant lesions, as hepatocellular carcinoma and hypervascular metastases (melanoma, kidney, adrenal
gland, GIST, sarcoma), and in benign lesions, as focal nodular hyperplasia, adenoma and, even, hemangioma.

We present our case of PEComa, in a 54-year-old woman, who underwent a routine abdominal ultrasound because of an incidental finding in a lumbar spine X-ray. Clinically, the patient had only lumbar pain and on physical examination no pathological signs were observed.

ULTRASOUND (US) SCANS showed a focal lesion in the right lobe of the liver (V segment); it was solid and heterogeneous, predominantly hypo to isoechoogenic, with an eccentric hyperechoic area and a central hypoechoic area. The margins was well-defined and it had an approximated size of 2.5 cm (Fig. 1 on page 14). Multiple hyperechoic lesions were documented in both kidneys, which were suggestive of angiomyolipomas (Fig. 2 on page 14).

Next, we performed a MULTIPHASE COMPUTED TOMOGRAPHY (CT) examination of the abdomen and pelvis after administration 100 ml of iodinated intravenous contrast material at an injection rate of 3 ml/second. Contrast-enhanced images were obtained at 30 seconds (hepatic arterial phase), 70 seconds (portal venous phase) and 300 seconds (delayed phase) after the initiation of contrast medium administration. No oral contrast medium was administered.

It confirmed the existence of a focal lesion in the right lobe of the liver (V segment), in contact with the hepatic capsule and very close to the right portal branch. Arterial phase CT showed the lesion as a heterogeneously hyperenhanced nodule in relation to the surrounding liver parenchyma with an eccentric low-attenuation area (Fig. 3 on page 15). On the portal venous (Fig. 4 on page 16) and delayed (Fig. 5 on page 17) phases, the tumor demonstrated progressive washout of contrast medium, except the marginal area, which turned progressively hiperattenuating. Capsule and central scar were not demonstrated. Macroscopic fat and calcifications were not observed. Neither lymphadenopathy nor portal vein involvement was present.

Moreover, the CT revealed a lot of lesions in both kidneys, solid and with homogeneous fat attenuating values, which were angiomyolipomas. The largest one was located in the left side, with 25 mm (Fig. 6 on page 18).

On MRI EXAMINATION, the lesion appeared hypointense on T1-weighted in-phase and out-of-phase images (Fig. 7 on page 19) and hyperintense on T2-weighted fast-spin-echo images with and without fat suppression (Fig. 8 on page 20). Dynamic MRI after bolus injection of 10 ml gadolinium with arterial (40 seconds), portal (75 seconds)
and delayed (180 seconds) phases was performed. On arterial phase, the mass showed prominent homogeneous enhancement except in an eccentric area, which remained unenhanced (Fig. 9 on page 21). On portal (Fig. 10 on page 22) and delayed phases (Fig. 11 on page 23), the lesion showed progressive wash-out and the eccentric area showed progressive enhancement.

Renal angiomyolipomas were also demonstrated on MRI (Fig. 12 on page 24).

The patient underwent a new MRI with a hepatobiliary contrast agent (gadoxetic acid -Gd-EOB-DTPA-). The enhancement pattern of the lesion was the same as the described previously. The hepatobiliary phase acquired 20 minutes after the contrast medium administration provides additional information; in this case, the lesion appeared homogeneously hypointense related to the surrounding liver parenchima (Fig. 13 on page 25).

According to the imaging findings, two main diagnoses were suggested: adenoma and hepatocellular carcinoma.

All analytic parameters to rule out the most common infectious processes, as echinococcus-specific IgG antibodies, hepatitis B surface antigen and hepatitis C virus antibody, was negative and the serum #fetoprotein level and other tumoral markers, as CEA, Ca 125 and Ca 19.9, remained within the normal range. Liver function test were also normal.

No history of neoplastic disease was known. No clinical evidence of tuberous sclerosis was present and there was no family history of cancer or known genetic disorders.

On this basis, the patient was considered to be indicated for surgical treatment.

During the operation, an INTRAOPERATIVE ULTRASOUND was performed, which displayed the mentioned lesion, and ruled out the presence of other lesions (Fig. 14 on page 26).

The surgical procedure consisted in a V hepatic segmentectomy with a cholecystectomy.

On gross examination, the lesion had decreased consistency, irregular margins, brownish-gray colour and hemorrhagic areas (Fig. 15 on page 27).
**Histologically**, the tumor showed spindle cells, with wide clear cytoplasms, arranged in solid nests and fascicles, closely related to the vascular channels. Cellular pleomorphism with atypia, high grade nucleus and conspicuous nucleolus were present. No atypical mitosis were observed. There was no evidence of fat or thick-walled vessels. ([Fig. 16 on page 28](#), [Fig. 17 on page 29](#) and [Fig. 18 on page 30](#)).

Grossly and microscopically, the surgical resection margins of the specimen were infiltrated by the lesion ([Fig. 19 on page 31](#)).

**Immunohistochemically**, the tumor cells demonstrated strong and diffuse positivity for MELAN-A, HMB-45, vimentin and smooth muscle actin ([Fig. 20 on page 32](#) and [Fig. 21 on page 33](#)), while estrogenic receptors and CD117 were weakly and focally positive, respectively. They were negative for S100 protein, CD 31, CD34 (endothelial marker), Hep-Par1, TTF-1, CK7, AE1/AE3, progesterone receptors and factor XIIIa ([Fig. 22 on page 34](#) and [Fig. 23 on page 35](#)). The lesion demonstrates a proliferative index with Ki-67 immunostaining of 10-15% ([Fig. 24 on page 36](#)).

Based on this specific immunophenotype profile, diagnosis of liver PEComa-NOS with unknown malignant potential was made.

The primary PEComa of the liver presented herein fulfills both the histologic and immunohistochemical diagnostic criteria, thus making it possible to rule out any other clear cell tumors without myomelanocytic differentiation (i.e., metastasis of renal and/or adrenal carcinoma). The absence of mature adipocytes, thick-walled blood vessels and dilated lymph vessels also makes it possible to rule out a misdiagnosis of angiomyolipoma or lymphangioniomyoma. Although our patient had a lot of renal angiomyolipomas associated, no association with tuberous sclerosis complex has been found.

The patient has not received adjuvant treatment and up to the present time, she has been followed up for seven months, with no evidence of either local recurrence ([Fig. 25 on page 37](#)), metachronic primary tumor, or distant metastases.
Images for this section:

**Fig. 1: ULTRASOUND EXAMINATION**

Routine ultrasound examination showed a focal solid lesion, with well-defined contours, hypoechoic, with an eccentric hyperchoic area (red arrow) and a central hypoechoic area (white arrow). The size was approximately 2.5 cm.
Multiple hyperechoic cortical lesions with well-demarcated margins were demonstrated in both kidneys, which were suggestive of angyomiolipomas. The largest one was localized in the left kidney with 30 mm of maximum diameter.

**Fig. 2: ULTRASOUND EXAMINATION**

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**Fig. 3: ABDOMINAL CT - ARTERIAL PHASE**

*Multiphase abdominal CT on arterial phase (A/B - from cranial to caudal) → heterogeneously hyperenhanced lesion (white arrow) compared with the surrounding liver parenchyma with an eccentric low-attenuation area (red arrow). It is localized in the right hepatic lobe (V segment).*

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Fig. 4: ABDOMINAL CT - PORTAL PHASE

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Multiphase abdominal CT on portal phase (A/B - from cranial to caudal) → Lesion (circle) is hardly identified; it is predominantly isodense respect to the surrounding parenchima, although hypo- (red arrow) and hyperdense (white arrow) areas are also demonstrated.
Fig. 5: ABDOMINAL CT - DELAYED PHASE

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Fig. 6: ANGIOMYOLIPOMAS IN BOTH KIDNEYS

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**Fig. 7: AXIAL T1-WEIGHTED MR IMAGES**

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**Fig. 8: T2-WEIGHTED MR IMAGES**

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*Axial T2-W Fast SE and Coronal T2-W Fast SE Fat-Sat MR images show a hyperintense lesion (red arrow) located in right hepatic lobe (V segment). No loss of signal intensity is observed. Note the lesion is very close to the right portal branch (white arrow).*
Fig. 9: DYNAMIC MRI - ARTERIAL PHASE

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Fig. 10: DYNAMIC MRI - PORTAL PHASE

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**Fig. 11:** DYNAMIC MRI - DELAYED PHASE

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Fig. 12: ANGIOMYOLIPOMAS IN LEFT KIDNEY

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Fig. 13: DYNAMIC MRI WITH Gd-EOB-DTPA

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Fig. 14: INTRAOPERATORY ULTRASOUND

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Fig. 15: MACROSCOPIC SPECIMEN

Specimen of hepatic segmentectomy with the lesion included. Gross appearance of the liver PEComa. The cut surface has a variegated appearance, including focal areas of necrosis.

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**Fig. 16: MICROSCOPIC FEATURES**

Hematoxylin-eosin, original magnification 2x (A) and 4x (B) → Neoplastic proliferation with cells arranged in solid nests and fascicles around numerous blood vessels.

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**Fig. 17:** MICROSCOPIC FEATURES

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**Fig. 18: MICROSCOPIC FEATURES**

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**Fig. 19: SURGICAL RESECTION MARGINS**

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Fig. 20: IMMUNOHISTOCHEMICAL FEATURES

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**Fig. 21: IMMUNOHISTOCHEMICAL FEATURES**

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Fig. 22: IMMUNOHISTOCHEMICAL FEATURES

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Fig. 23: IMMUNOHISTOCHEMICAL FEATURES

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Fig. 24: IMMUNOHISTOCHEMICAL FEATURES

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The tumor demonstrates a proliferative index with Ki-67 immunostaining of 10-15%.
Fig. 25: FOLLOW-UP ABDOMINAL CT

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Conclusion

- PEComa-NOS of the liver is a rare mesenchymal tumor without typical imaging findings.

- These tumors should be regarded as tumors with uncertain biological potential until definite criteria for evaluating the malignant behaviour will have been determined.

- All unusual carcinomas and mesenchymal tumors of the liver should be tested for HMB-45: when positive, there is a high likelihood of a PEComa.

- There is a strong necessity to report every particular case of liver PEComa in order to improve our general knowledge about the incidence, natural course and imaging findings.

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