Case Report

Hepatic epithelioid angiomyolipoma: a case report

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ABSTRACT

Angiomyolipoma (AML) is a rare benign solid tumor, of mesenchymal origin. Angiomyolipomas can be subdivided, according to their predominant component. The predominance of epithelioid cells characterizes the epithelioid variant (EAML). These express a more aggressive clinical behaviour with a greater potential for malignant transformation. In the absence of specific radiological features, the diagnosis of hepatic EAML depends on the pathological and immunohistochemical study. We present the case of an 80 years old female with a computed tomography (CT) scan showing a hepatic nodule at the transition of segments 5 and 8, and a left kidney nodule previously biopsied and confirmed to be a renal angiomyolipoma. A liver nodule biopsy was performed, whose histology revealed a probable gastrointestinal stromal tumor (GIST). The patient underwent a 5/8 subsegmentectomy and pathology report revealed epithelioid angiomyolipoma. After discussion of the case in the multidisciplinary tumor board, it was decided to perform a left nephrectomy, whose pathology revealed leiomyomatous angiomyolipoma. No further treatment and surveillance on outpatient clinic were decided. Hepatic EAML is a rare lesion that, although mostly benign, can exhibit malignant behavior with distant metastasis and local invasion. Its identification is of paramount importance. The definitive diagnosis is only possible through histological and immunohistochemical analysis. Additional studies are needed in order to establish diagnostic criteria and predictive characteristics of malignancy.

Keywords: Epithelioid angiomyolipoma, PEComa, Liver, Immunohistochemical staining

INTRODUCTION

Benign liver lesions can originate from hepatocytes, examples of which are focal nodular hyperplasia, regenerative nodular hyperplasia or hepatocellular adenoma. Fibrous tumors, hemangiomas and smooth muscle tumors originate from mesenchymal cells.1 Angiomyolipoma (AML) is a rare benign solid tumor, of mesenchymal origin, made up by varying proportions of adipose tissue, smooth muscle and vascular structures. According to the World Health Organization (WHO), since 2002 this benign tumor has been part of epithelioid perivascular neoplasms, generically referred to as perivascular epithelioid cell neoplasms (PEComas).2 This family of neoplasms includes renal and extra-renal AMLs, clear cell or extra-pulmonary tumor, linfoangiomymatosis and clear cell myelomelanocytic tumors of the falciform ligament.1 PEComas are considered extremely rare lesions when they appear in locations other than lung or kidney. Angiomyolipomas can be subdivided, according to their predominant component, into epithelioid, fusiform or intermediate. The epithelioid variant of AML (EAML) is characterized by the predominance of epithelioid cells, and these tumors express a more aggressive clinical behavior with a greater potential for malignant transformation.3 There are no pathognemonic clinical, laboratory or radiological characteristics of the EAML, so more than 70% of cases fail to be diagnosed.4 In this context, EAML...
of the liver is often confused with other liver lesions of benign or malignant etiology, such as hepatocellular carcinoma (HCC), hepatic adenoma, leiomyoma, hepatoblastoma, melanoma and GIST.\textsuperscript{3} In the absence of specific radiological characteristics, the diagnosis of hepatic EAML depends on the pathological and immunohistochemical study, according to the expression of smooth muscle and melanocytic markers.

This article intends to review the state of the art regarding the diagnosis and management of this type of lesions, based on a clinical case.

**CASE REPORT**

We present a case of an 80 years old female, referred from Hepatology clinic for liver nodule diagnosed on computed tomography (CT) in the context of an abdominal pain investigation. CT showed a 30×23 mm nodule at the transition of segments 5 and 8, near the right anterior portal pedicle. CT also revealed the presence of a known left kidney nodule measuring 30×22×33 mm previously biopsied and confirmed to be a renal angiomyolipoma. (Figure 1).

For further study, a liver nodule biopsy was performed. Histology revealed a probable gastrointestinal stromal tumor (GIST). Looking for a primary location, a PET was ordered, confirming a high-grade metabolic activity hepatic nodule and a low-grade metabolic activity kidney nodule. Suspecting of a primary hepatic GIST, liver resection was proposed. The patient was submitted to an open 5/8 subsegmentectomy and cholecystectomy (Figure 2). Parenchyma transection was undertaken with ultrasonic aspirator and hemostasis with bipolar energy, under intermittent Pringle maneuver. The postoperative period was complicated by a urinary tract infection, and the patient was discharged on the 10th postoperative day.

The pathology report revealed epithelioid angiomyolipoma without mitotic activity or areas of necrosis, with a proliferative index (Ki67) of 15%, with positivity for actin, melan A, and CD34. The lesion showed an absence of immunostaining for C-Kit, HepPar1, and AE1/AE3 (Figure 3 and 4). Considering the hypothesis of metastatic liver lesion in relation to possible primary of the left kidney, the case was discussed in the multidisciplinary tumor board, deciding on left nephrectomy. Thus, the patient underwent an open retroperitoneal left nephrectomy, which was uneventful. Pathology revealed leiomyomatous angiomyolipoma of the kidney, positive for CD34 and Melan A. No further treatment and surveillance on the outpatient clinic were decided.
DISCUSSION

AML is a tumor of mesenchymal origin being the kidney its most frequent location. The hepatic localization of these lesions is extremely rare. It is a more frequent entity in women, in a 5:1 ratio, with a higher prevalence between 30 and 65 years. Asymptomatic in more than half of the cases, the diagnosis is mostly incidental. Symptoms appear in relation to the size of the lesions, which can condition pain, abdominal distension or early satiety. Rare cases of tumor rupture or necrosis are also described in the literature, essentially in larger lesions. In these cases, they present as an emergency, with severe abdominal pain and shock.

As mentioned above, the AML epithelioid variant (EAML) consists of a triad of tortuous and thickened blood vessels, smooth muscle cells and adipose tissue. The great variability of the proportion of each of these EAML components makes its radiological diagnosis very difficult. Generally, the definitive diagnosis is only possible through the histological analysis of the specimen and/or with immunohistochemical tests. Differential diagnoses include other liver hypervascular lesions, whether benign or malignant behavior, such as hepatic adenoma, focal nodular hyperplasia, GIST, hepatocarcinoma or sarcoma, among others. Most lesions present as solitary nodules with regular and well-defined edges. On ultrasound, most cases present as heterogeneous hypoechoic lesions. On CT, EAML presents itself as a hypodense lesion, showing moderate to intense uptake of contrast in the arterial phase with attenuation of uptake during the portal and late phases. When observed in magnetic resonance imaging (MRI), EAML is a heterogeneous hypointense lesion in T1 and more hyperintense in T2, also showing contrast uptake in the arterial phase. Due to the contrast uptake characteristics, the main differential diagnosis of EAML is made with hepatocarcinoma, and 60% of patients with hepatic EAML are diagnosed with hepatocarcinoma preoperatively. There are few studies regarding the characteristics of these lesions demonstrated in PET-FDG. Generally, EAML has a hypermetabolic behavior, which, as in the case described, shows high uptake in PET.

Although the radiological characteristics may provide some important information, the definitive diagnosis is only possible through the histological analysis of the resected specimen in conjunction with an immunohistochemical study. The predominance of epithelioid cells is the most important factor for the diagnosis of EAML. With regard to immunohistochemical analysis, and as part of the PEComa family, EAML includes bidirectional differentiation into melanocytic and smooth muscle cells. In this sense, these lesions reveal positivity for markers of melanocytic lineage (HMB-45 and Melan A) as well as markers of the myoid lineage (Actin and SMA). EAML is the only liver tumor that marks positively for HMB-45 and Melan A, being the first marker the most sensitive for the diagnosis of these lesions. When there is a predominance of vascular structures, these lesions are also positive for CD34. Regarding the differential diagnosis with GIST, these lesions express the c-Kit marker, a negative marker in the case described. Most hepatic AMLs have a benign behavior, however, there have been reported cases of tumor growth, local recurrence after surgical resection, vascular invasion and adjacent liver parenchyma and distant metastasis. Epithelioid tumors are those that most often develop malignant behavior. Folpe et al determined some histological properties capable of conferring a greater risk of malignancy: lesions greater than 5 cm; infiltrative lesions, with high cellularity; number of mitotic figures above 1/50 per field; necrosis and vascular invasion. Although malignancy criteria are not universally defined to date, many authors consider that PEComas that demonstrate two or more of these factors should be considered malignant. In the case reported, the histological analysis excluded the presence of any worrisome features, and this lesion was considered benign.

Since there are no pathognomonic characteristics for a more definitive radiological diagnosis, many of these lesions end up being proposed for surgical resection, which the definitive treatment is in case of confirmed hepatic EAML. The biopsy of the lesion can be useful in confirming diagnosis, and in the presence of epithelioid cells, surgical resection should be indicated. In about 10% of resected patients, local recurrence or distant metastasis occurs, essentially in lung, diaphragm and mesentery. Although some literature considers the hypothesis of conservative treatment in lesions smaller than 5 cm, whose biopsy confirms the presence of EAML with normal liver function, more recent cases of aggressive behavior come to question this attitude, reserving it for older patients or those with morbidities that contraindicate surgical treatment. Given the possibility of malignant behavior, many authors consider that all hepatic EAMLs should be considered as lesions of uncertain malignant potential and, after surgical resection, a rigorous follow-up as to be done.

The nuances of this case reside in the fact that we were faced with a benign renal lesion and an unrelated liver lesion thought to be a primary GIST. With that information a decision to resect the liver lesion for its malignant potential was made. As the liver lesion histology revealed to be a potentially malignant AML, and as primary liver EAML is such a rare finding, doubt about the benign nature of the renal AML ensued and that was the rationale for kidney resection. The overall final findings leave us with a benign kidney AML and a potentially malignant liver EAML, unrelated.

CONCLUSION

Hepatic EAML is a rare lesion, of mesenchymal origin and belonging to the PEComa family. These lesions, although mostly benign, can exhibit malignant behavior with distant metastasis and local invasion. Thus, its identification is of
paramount importance, both for the establishment of surgical treatment and for the definition of follow-up and surveillance strategies. Although the radiological characteristics may raise suspicion, the definitive diagnosis is only possible through histological and immunohistochemical analysis. In addition to a definitive diagnosis, histological analysis can identify the presence of worrisome features that can predict the lesion’s malignancy potential so that more restricted follow-up strategies can be adopted. Additional studies are needed in order to establish diagnostic criteria and predictive characteristics of malignancy in order to adapt and define therapeutic and surveillance strategies.

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