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Multicentric angiomyolipoma in kidney, liver, and lymph node: case report/review of the literature

Angiomiolipoma multicêntrico em rim, fígado e linfonodo: relato de caso/revisão da literatura

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ABSTRACT

Introduction: The angiomyolipoma (AML) is constituted by adipose tissue, blood vessels and smooth muscle fiber; follows a benign clinical course, with slow growth and absence of metastasis, occurring in tuberous sclerosis or sporadically. **Objective:** We intend to describe the clinical, radiological and histological aspects of this tumor. **Case report:** A-64-year-old woman presented with abdominal pain and dyspepsia. Tomography showed hepatic, renal and mesenteric nodules. Histological evaluation of mesenteric lymph node revealed perivascular epithelioid differentiation neoplasia, compatible with AML/perivascular epithelioid cell tumor (PEComa), positive for anti-S100, anti-human melanoma black-45 (HMB-45) and anti-smooth muscle actin. **Conclusion:** We described a rare AML with renal, hepatic and lymph node involvement, representing a multicenter version instead of metastasis.

Key words: angiomyolipoma; tuberous sclerosis; perivascular epithelioid cell neoplasms.

INTRODUCTION

The angiomyolipoma (AML) is a benign tumor composed of three different kinds of tissue: adipose tissue, blood vessels and smooth muscle fibers. It represents 1%-3% of all renal tumors, and may occur as part of the tuberous sclerosis complex (TSC), or sporadically. TSC is a dominant autosomal multisystem disorder, of low incidence, which provokes benign tumors in kidneys, skin, brain, lungs, heart and eyes, characterized by the classic triad: epilepsy, mental retardation, and sebaceous adenomas[1-3].

AML is mostly asymptomatic, and accidentally diagnosed, but it may present with abdominal pain, palpable abdominal mass, lumbar pain, and severe hematuria, besides other consequences of intratumoral hemorrhage[3, 4].

The suggestion of AML diagnosis may be offered by a combination of imaging exams, such as ultrasonography (USG), computed tomography (CT) and magnetic resonance (MR), which evidence the fat tissue present in the mass; but renal cell carcinoma is an important differential diagnosis. Diagnosis is confirmed by biopsy and histopathological analysis with immunohistochemistry[1, 5].

We describe a rare case of AML with simultaneous renal, hepatic and lymph node involvement, which may be confounded with metastatic tumors.

CASE REPORT

A 64-year-old female patient presented with mild abdominal pain and dyspepsia. She denied weight loss. Upper abdomen CT evidenced several hypodense nodules in the liver and both kidneys, possibly corresponding to AML, besides oval expansile lesion with soft tissue density and intense contrast enhancement, intermingled with small areas of necrotic degeneration, measuring 2.9 × 2.5 cm, located in the mesentery (**Figure 1**).

The mesenteric lymph node was resected and histopathologically studied. The study revealed a neoplasm composed of smooth muscle cells, mature adipocytes and blood vessels with thickened walls. The smooth muscle cells exhibited

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moderate pleomorphism; some had a spindle-shaped aspect; others, an epithelioid aspect, oval. Mitotic activity and necrosis were not observed (**Figures 2** and **3**). Immunohistochemistry identified a neoplasm with perivascular epithelioid cell differentiation (myomelanocytic) compatible with AML/perivascular epithelioid cell tumor (PEComa), positive for antibodies anti-S100, anti-smooth muscle actin (**Figure 4**), and anti-human melanoma black-45 (HMB-45) (**Figure 5**). The patient's postoperative period was uneventful, and she was kept on clinical follow-up only. Investigation of other diseases (cerebral, pulmonary, pancreatic and cardiac) ruled out the clinical diagnosis of TSC. Genetic study for *TSC1* and *TSC2* genes was not performed.

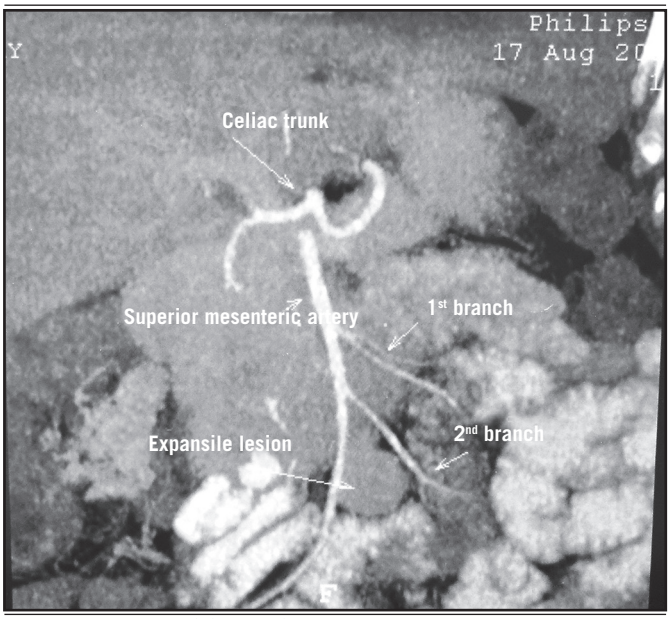

FIGURE 1 – *CT: expansile lesion in the mesentery*
CT: computed tomography.

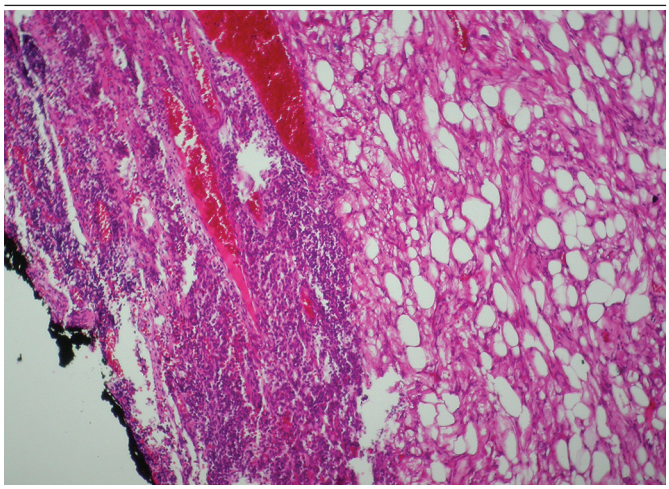

FIGURE 2 – *Photomicrograph (HE staining, 10× objective lens): residual lymphoid tissue on the left and neoplasm on the right*
HE: hematoxylin and eosin.

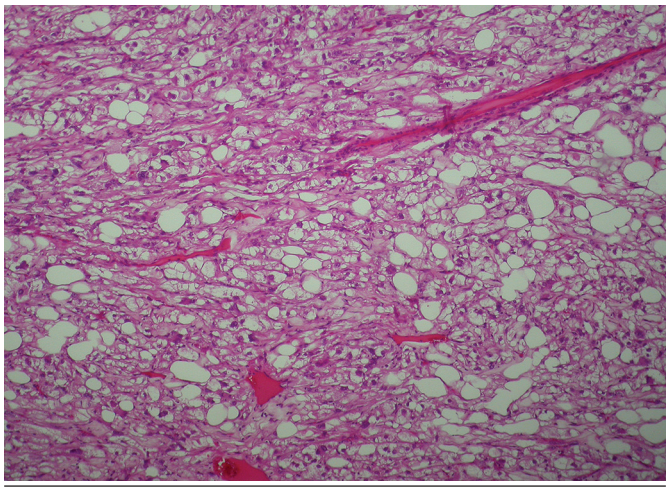

FIGURE 3 – *Photomicrograph (HE staining, 10× objective lens): three lineages in the neoplasm – adipose cells, blood vessels and epithelioid muscle cells*
HE: hematoxylin and eosin.

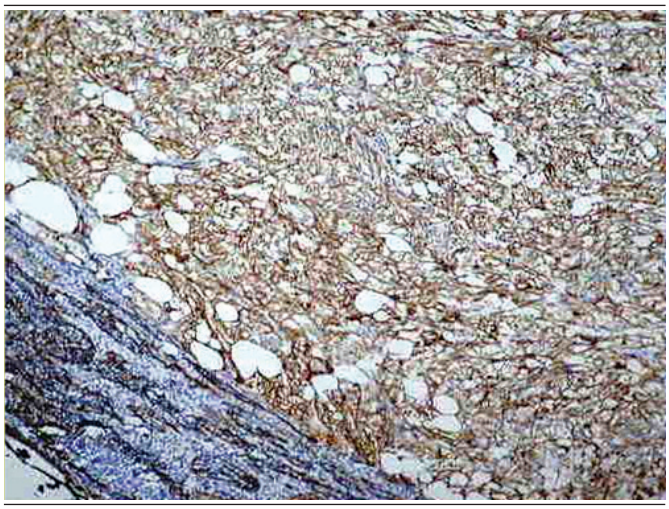

FIGURE 4 – *Immunostaining for anti-smooth muscle actin antibodies (10× objective lens)*

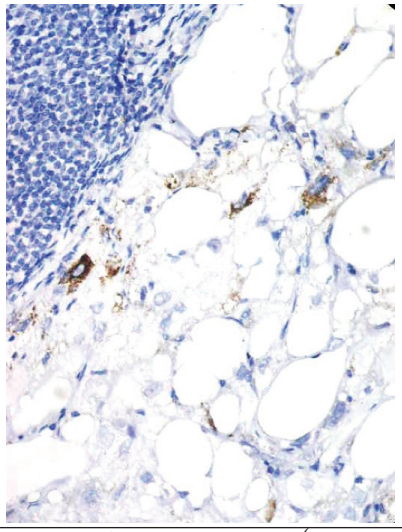

FIGURE 5 – *Immunostaining for anti-HMB-45 antibody (40× objective lens)*
HMB-45: human melanoma black-45.

DISCUSSION

AMLs are infrequent tumors that represent 3% of solid renal masses. Most of them occur sporadically (80%), often in middle-aged adults, with a strong predilection for women (F:M = 4:1). The other 20% are associated with phakomatoses, such as tuberous sclerosis, neurofibromatosis, von Hippel-Lindau disease and Sturge-Weber syndrome[2, 3].

Morphologically, AML belongs to the family of PEComas, defined by the World Health Organization (WHO) as "mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells" (PECs). The typical AML lesion exhibits triphasic histology, with tortuous blood vessels with thickened walls, PECs of myoid appearance arranged in nests or bundles, and lipid-filled PECs that resemble adipocytes. However, the proportion of these different cell types is highly variable[6].

PECs are a cell type constantly present in a group of tumors, including AML, the clear-cell "sugar" tumor of the lung and extrapulmonary sites, lymphangioleiomyomatosis, clear-cell myomelanocytic tumor of the falciform ligament, and rare clear-cell tumors of other anatomic sites. They have distinct morphological, immunohistochemical, ultrastructural and genetic features; and are characterized by typically perivascular location, with mild or no atypia. Immunohistochemically, they express both myogenic and melanocytic markers, such as HBM-45, human melanosome-associated antigen-1 (HMSA-1), melanoma antigen recognized by T-cells 1 (Melan-A or Mart-1), microphthalmia-associated transcription factor (Mitf), actin, and desmin[7].

PEComas have been described in different organs. In the kidney, they include several forms of AML: classic, microscopic, cystic, epithelioid and oncocytoma-like. The classic form is the most common mesenchymal tumor of the kidney[8].

The renal AML is seen in normal individuals, but occurs more frequently in patients with the genetic disease TSC, where incidence in adults is around 70%. Renal AMLs of TSC patients are found in both sexes, in the third and fourth decades of life, with predominance in females. They are asymptomatic, multiple and bilateral, but each of these characteristics is uncommon or rare in individuals without TSC, as was the described case (multiple bilateral renal AMLs). Sporadic AMLs occur in older patients, in the fourth to sixth decades of life, and they are single, unilateral and larger than those associated with TSC[7]. In a recent series from a single institution, none of the 32 non-TSC patients with renal AML had bilateral AML[6].

Tuberous sclerosis is a dominant autosomal syndrome of hereditary transmission, in which there is mutation on chromosomes 9 and 16, in *TSC1* (9q34) and *TSC2* (16p13.3) genes, respectively[8]. It is characterized by mental retardation, seizures, and cell proliferations (AML, subependymal giant cell tumors, cutaneous angiofibromas, cardiac rhabdomyomas, lymphangioleiomyomatosis and pulmonary multifocal micronodular hyperplasia). Similar alterations of TSC genes have been demonstrated in a significant number of PEComas, occurring both in TSC and in sporadic cases[1, 3, 4, 9, 10].

The origin and genetic basis of AML are uncertain. AML and other PEComas express several proteins whose expression is typical of melanocytes, including GP100 silver, the antigen detected by the HBM-45 monoclonal antibody, suggesting that the development or the genetic basis of these neoplasms may be related to normal or aberrant melanocytic development. This characteristic, combined with that of the smooth muscle cell, suggests that they may have their origin in the neural crest. In AMLs that occur in TSC, there is evidence of biallelic inactivation of *TSC1* or *TSC2* gene, corresponding to the mutation present in these individuals[6].

Few studies were carried out to analyze the genetic basis of AML development in non-TSC individuals. Loss of heterozygosity (LOH) in the TSC2 region has been reported, but not consistently[11]. The frequency of TSC1 and TSC2 involvement in the development of PEComas is still not defined, due to the small number of examined cases and inconsistency of the findings. The consistent activation of the mammalian target of rapamycin (mTOR) pathway in these tumors has been documented[6, 12].

Renal AML is frequently an incidental finding in imaging diagnostic tests. When AMLs are symptomatic, they usually present clinically with abdominal or lumbar pain, which are the main symptoms, besides hematuria, hemorrhage, anemia, systemic arterial hypertension, fever, renal failure, palpable mass, and urinary infection. Their main clinical meanings are: large lesions prone to spontaneous hemorrhage (more common when they are > 4 cm), what occurs in around 25% of the patients, with intense abdominal pain and shock[13, 14]; progressive lesions that may affect the renal function; and fat-poor AML, because they are difficult to distinguish from other renal neoplasms[6].

Most AMLs occur in the renal parenchyma, but may affect other organs, such as liver, spleen, uterus, uterine tubes, lips and lymph nodes (described in our case). Besides the kidney, the liver is the organ more frequently involved by AML, both the classic and the epithelioid types[7].The presence of tumors in extra renal sites is considered multicentric, not metastatic disease[2, 3, 10].

The diagnosis of AML may be reached by the association of imaging exams and histopathology. CT has important technical parameters for the diagnostic assessment of solid renal tumors, and may identify foci of tissue with fat attenuation, linear vascularization, hematoma and aneurysmatic dilatation, that are consistent with this kind of tumor. Histopathology and subsequent immunohistochemical study evidence positivity for anti-S100, anti-HMB-45, and anti-smooth muscle actin antibodies in great part of the cases[3-5, 10, 15]. In the described case, the diagnosis of hepatic and renal AML was based on radiology; just the mesenteric lymph node was removed and analyzed morphologically.

The classic AML has a benign prognosis. Multifocality and regional lymph node involvement may occur, what is considered multifocal growth pattern, not metastasis[7].

Some questions remain about PEComas: their histogenesis and the normal/physiological counterpart; the definition of epithelioid AML; and the identification of histological criteria of malignancy[8].

Malignant PEComa can be quite aggressive, leading to multiple metastases and death, as expected with a high-grade sarcoma. Tumor size > 5 cm, infiltrative growth pattern, high nuclear grade, necrosis and mitotic activity > 1/50 high-power field (HPF) have been associated with aggressive clinical behavior[7].

The recommended management of AML may be challenging, depending on its size, symptoms, complications and association or not with TSC. The treatment objective is preservation of renal function, thus one may opt for arterial embolization of the tumor, ablation by radiofrequencies, and surgeries with maximal preservation of renal tissue[2, 6, 13, 14, 16]. Rapamycin is an mTOR-specific inhibitor, approved in the United States for treatment of renal cell carcinoma and acute myeloid leukemia. Therapeutic studies have been performed on the use of this drug for treating PEComas[7].

CONCLUSION

As in the literature, the present case demonstrates AML as a multicentric, not a metastatic disease, affecting simultaneously kidneys, liver, and mesenteric lymph node. The diagnosis of the disease is based mainly on imaging exams and histopathology; the treatment is aimed at maximal preservation of renal parenchyma.

RESUMO

Introdução: *O angiomiolipoma (AML) constitui-se de tecido adiposo, vasos sanguíneos e fibras musculares lisas; tem curso clínico benigno, crescimento lento e ausência de metástases, ocorrendo no complexo esclerose tuberosa ou esporadicamente.* ***Objetivo:*** *Objetivamos descrever aspectos clinicorradiológicos e histológicos desse tumor.* ***Relato do caso:*** *Paciente do sexo feminino, 64 anos, com dor abdominal e dispepsia. Tomografia mostrou nódulos hepáticos, renais e mesentéricos. Exame histopatológico de linfonodo mesentérico evidenciou neoplasia com diferenciação epitelioide perivascular condizente com AML/neoplasias de células epitelioides perivasculares (PEComa), positiva para anti-S100, anti-human melanoma black-45 (HMB-45) e antiactina de músculo liso.* ***Conclusão:*** *Descrevemos raro envolvimento simultâneo renal, hepático e linfonodal por AML, representando versão multicêntrica, e não doença metastática.*

Unitermos: *angiomiolipoma; esclerose tuberosa; neoplasia de células epitelioides perivasculares.*

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