Perivascular Epithelioid Cell Tumor: A Case Report of a Rare Entity

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Abstract

Perivascular epithelioid cell tumor is a rare mesenchymal tumor with myomelanocytic differentiation. It mainly occurs in middle-aged females and can be found at any location. The differential diagnosis is broad but the immunohistochemical biomarkers establish the diagnosis. A 4-year-old girl was referred to a pediatric gastroenterology clinic due to recurrent umbilical pain and the workup revealed biliary lithiasis. She remained in follow-up, asymptomatic, no physical findings, and stable ultrasound. Six years later, a supra-umbilical mass was detected by ultrasound, and the magnetic resonance imaging revealed a highly vascularized intra-peritoneal tumor with well-defined limits. Surgical mass resection was performed, and the histology revealed morphological and immunohistochemical aspects of a perivascular epithelioid cell tumor of the abdominal wall. Given the size of the lesion (> 5 cm) and admitting uncertain malignant potential, she was submitted to margin enlargement. Four years later, she remains asymptomatic without clinical or imagiological evidence of relapse.

Keywords: Incidental Findings; Perivascular Epithelioid Cell Neoplasms/diagnosis; Perivascular Epithelioid Cell Neoplasms/surgery; Abdominal Wall; Treatment Outcome

Introduction

Perivascular epithelioid cell tumors (PEComas) are a family of rare mesenchymal neoplasms that are characterized by peculiar morphological and immunohistochemical features. According to the current World Health Organization classification of soft tissue tumors, they are considered tumors of uncertain differentiation, including benign and malignant types.[1]

Perivascular epithelioid cell tumors are composed of distinctive epithelioid cells that are closely associated with blood vessel walls, coexpressing melanocytic and smooth muscle biomarkers. They show a wide anatomical distribution usually presenting as painless masses and mainly occurring in females (ratio 1:7) with an average age of 45 years.[1,2] While surgical resection may suffice to manage isolated tumors, when facing metastatic disease or unresectable lesions, inhibitors of the mammalian target of rapamycin (mTOR) can be an effective treatment.[3]

Case Report

A previously healthy 4-year-old girl was referred to a pediatric gastroenterology clinic due to recurrent umbilical pain, without any other symptoms. During workup, an abdominal ultrasound revealed two 4mm gallstones without dilation of the biliary tract. The etiological investigation was inconclusive, with no identifiable underlying cause of lithiasis (hematological, metabolic, infectious, pharmacological, or malformative). She remained in follow-up, asymptomatic, and without physical findings. Annual abdominal ultrasound was performed and remained stable. At the age of 10, a supra-umbilical mass was accidentally detected on ultrasound. The magnetic resonance imaging revealed an intra-peritoneal tumor (50 x 40 x 45 mm) at umbilical level with well-defined limits, heterogeneous, predominantly solid, highly vascularized, and compressing inferior vena cava with no apparent local invasion. A computed tomography angiography (angio-CT) was also performed, without unmistakable signs of local invasion and vascularization predominantly from the lower epigastric vessels (Fig. 1). After that, a laparotomy was performed for total macroscopic mass resection (Fig. 2). The histological examination revealed morphological aspects of a

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PEComa of the abdominal wall, with neither atypia, nor vascular invasion (Fig. 3). The mass was composed of spindle-to-epithelioid cells with clear-to-eosinophilic cytoplasm arranged around blood vessels without high nuclear grade areas or necrosis. Immunohistochemical biomarkers were positive for smooth muscle actin (SMA), vimentin, human melanoma-black-45 (HMB45), melanoma antigen (MelanA), and S100 protein. The proliferative index (ki67) was low (5%-10%) but there was at least one mitosis per 50 high power fields (HPF) and the surgical margin was positive (R1). She was referred to a pediatric oncology center and, given the size of the lesion (> 5 cm) and the presence of mitoses, it was classified as a malignant PEComa. She was submitted to margin enlargement, which showed no residual tumor. No adjuvant treatment was delivered. The follow-up was done with ultrasound every three months for the first year after surgery, then every four months for another year and then every six months. Four years later, she remains asymptomatic without clinical or imagiological evidence of relapse.

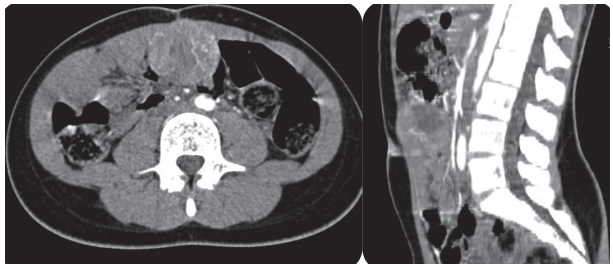

Figure 1. Abdominal computed tomography angiography (angio-CT) revealing an umbilical intra-peritoneal tumor (50 x 40 x 45 mm) with well-defined limits, heterogeneous, predominantly solid, highly vascularized, predominantly from the lower epigastric vessels.

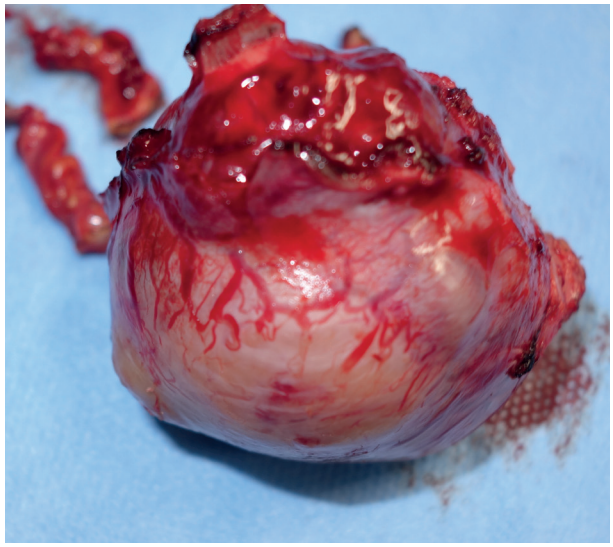

Figure 2. Surgical sample. Nodular capsulated tumor measuring 70 x 55 x 45 mm. The outer surface was congested, with visible engorgement of the vessels and a fluctuating consistency. At cut, it was white, solid, of friable consistency, with hemorrhagic areas.

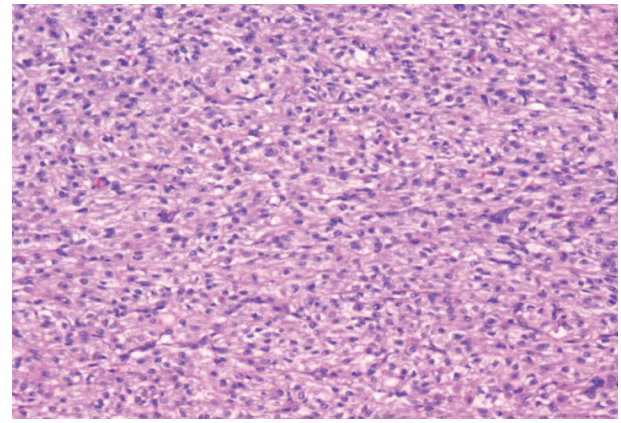

Figure 3. Histopathological analysis with medium cellularity composed of spindle-to-epithelioid cells with clear-to-eosinophilic cytoplasm arranged around blood vessels. One or more mitoses per 50 HPF. The neoplastic cells were positive for smooth muscle actin (SMA), vimentin, human melanoma-black-45 (HMB45), melanoma antigen (MelanA), and S100 protein. There were no high nuclear grade areas, necrosis nor lympho-vascular invasion.

Discussion

PEComas were first defined by Bonetti et al[4] as being composed of perivascular epithelioid cells (PECs). They hypothesized that PEC could modulate its morphology and immunophenotype and that PEComa family tumors were composed of PECs in different stages of modulation. What is known so far is that PEComas are characterized by myomelanocytic differentiation but neither a precursor lesion nor a cell of origin have been identified yet.[5] In 2002, the World Health Organization accepted the designation PEComa as a mesenchymal neoplasm composed of histologically and immunohistochemically distinctive epithelioid or spindle cells, co-expressing myogenic and melanocytic markers.[6] The cells are typically arranged around blood vessels and appear to form the vessel wall, often infiltrating the smooth muscle of small to medium-sized vessels. Periluminal cells are usually epithelioid and the more peripheral cells are spindle-shaped, both types with small, centrally located round to oval nuclei with inconspicuous nucleoli, although there is sometimes focally marked nuclear atypia. The cytoplasm is clear or eosinophilic, and sometimes there is clear cell change adjacent to a perinuclear eosinophilic zone. Rarely, there can be prominent melanin pigmentation. Fatty change can be seen, especially in the peripheral cells, which can mimic lipoblasts.[7] Perivascular epithelioid cell tumors can be virtually found at any location but most often arise in the uterus (40%), retroperitoneum, abdominopelvic region, and gastrointestinal tract.[1,8,9] Data on PEComa arising in the abdominal wall remain limited to only a few case reports in the literature to the best of our knowledge.[10-14]

The differential diagnosis is fairly broad and can include carcinomas, smooth muscle tumors, and adipocytic neoplasms, but the immunohistochemical co-expression of melanocytic (HMB45) and smooth muscle (desmin, SMA, and/or muscle-specific actin) biomarkers establish the diagnosis.[2] Over 50% of them also stain for MelanA, even in the absence of HMB45. Some cases stain for S-100 protein that must be differentiated from melanomas.[15]

Perivascular epithelioid cell tumors may behave indolently but entail variable malignant potential with the most common metastatic sites being the liver, lymph nodes, lungs, and bone.[1] The categorization of PEComas was proposed into three groups based on tumor diameter, nuclear grade and cellularity, mitotic rate, necrosis, vascular invasion, and infiltrative growth. Based on these criteria, PEComas should be considered potentially malignant in case of displaying two or more of the following features[16]:

- Size > 5 cm;
- Infiltrative growth;
- High nuclear grade and hypercellularity;
- One or more mitoses per 50 HPF;
- Necrosis;
- Vascular invasion.

Cases that have nuclear atypia or exceed 5 cm in diameter but lack significant mitotic activity and necrosis after thorough sampling can be regarded as of uncertain malignant potential and followed up closely.[7] According to the mentioned criteria, our patient had two malignant risk factors: the large diameter (> 5 cm) and ≥ 1 mitoses per 50 HPF.

Presently, when there is no evidence of metastasis, surgical resection is the recommended approach.[17] The benefits of chemotherapy or radiation have not been established thus far. However, there have been recent advances in the therapy of malignant PEComas related to increased knowledge of specific genetic changes and their effects on metabolic pathways.[18] Specifically, mutations with a loss of function of the tuberous sclerosis complex (TSC1/TSC2) appear to play an important role on the genesis of these neoplasms, by upregulating the mTOR metabolic pathway, leading to proliferation and increased cell growth. Therapies targeting the mTORC pathways, like the mTORC1 inhibitor sirolimus, have shown to produce meaningful clinical responses in these patients.[19-20]

In addition, a small subset of PEComas harboring rearrangements of the *TFE3* (*Xp11*) gene locus has been identified.[21] This subgroup is characterized by an epithelioid phenotype and attenuated or missing expression of myogenic markers, presenting an elevated transcriptional activity of *TFE3* and subsequent induction of pro-oncogenic pathways (c-Met, AKT, mTOR).[22-23]

Given the rarity of these tumors and the limited available data, a precise estimation of the objective response rate and median progression-free survival is difficult to be measured. A study with 53 adult patients compared the cytotoxic chemotherapy regimens with antiangiogenics and mTOR inhibitors, showing the last as the most active agents with an objective response rate of 41% and a median progression-free survival of nine months. Vascular endothelial growth factor receptor inhibitors and chemotherapy with gemcitabine or anthracycline-based regimens are options in further line, but with a lower response rate and progression-free survival.[24]

Since mTOR signaling can be regarded as the tumor driver in most of the cases and according to the available evidence, a treatment with sirolimus may be considered for our patient, in case of recurrence.

With this case report, we intend to recall the importance of considering this rare etiology in the evaluation of a soft tissue tumor and enhance the importance of immunohistochemical biomarkers for the definitive diagnosis. The correct histological classification is essential to assess the potential of malignancy and thereby ensure the most appropriate therapeutic approach.

WHAT THIS CASE REPORT ADDS

- Perivascular epithelioid cell tumors are a broad family of rare mesenchymal neoplasms composed of perivascular epithelioid cells characterized by myomelanocytic differentiation.
- Immunohistochemical techniques play a major role in the diagnosis of perivascular epithelioid cell tumors.
- Perivascular epithelioid cell tumors may behave indolently but entail variable malignant potential.
- In the absence of metastasis, surgical resection is the recommended approach.
- Mammalian target of rapamycin inhibitors can be considered in case of recurrence or in large, inoperable tumors.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

This clinical case was presented at the European Academy of Paediatrics 2019 Congress and Mastercourse, September, Porto, Portugal

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Um Caso Clínico Raro de Tumor de Células Epitelioides Perivascular

Resumo

O tumor de células epitelioides perivasculares é um tumor mesenquimatoso raro com diferenciação miomelanocítica. Afeta sobretudo mulheres de meia-idade e pode ser encontrado em qualquer localização. O diagnóstico diferencial é vasto, mas os biomarcadores imunohistoquímicos permitem estabelecer o diagnóstico. Uma criança de 4 anos, do sexo feminino, foi referenciada à consulta de gastroenterologia por dor abdominal recorrente, sendo que a investigação revelou litíase biliar. Durante o seguimento manteve-se assintomática, sem alterações à observação e ecografias sobreponíveis. Seis anos depois, uma massa supra-umbilical foi detetada na ecografia abdominal e a ressonância magnética nuclear revelou um tumor intra-peritoneal com limites bem definidos e muito vascularizado. Foi submetida a resseção tumoral cirúrgica e o exame histológico evidenciou aspetos morfológicos e imunohistoquímicos de um tumor de células epitelioides perivasculares da parede abdominal. Dado o tamanho da lesão (> 5 cm) e admitindo potencial maligno incerto, foi realizada cirurgia de alargamento das margens. Quatro anos depois, mantém-se assintomática e sem evidência clínica ou imagiológica de recidiva.

Palavras-Chave: Achados Incidentais; Neoplasia de Células Epitelioides Perivasculares/diagnóstico; Neoplasia de Células Epitelioides Perivasculares/cirurgia; Parede Abdominal; Tratamento