CASE REPORT

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Peritoneal Perivascular Epithelioid Cell Tumor with Pulmonary Metastasis

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ABSTRACT Perivascular Epithelioid Cell Tumor (PEComa) is part of an extremely rare family of mesenchymal tumors. We present a case of Peritoneal Pecomatosis with pulmonary metastases in a 35-year-old woman, with previous multiple myomectomies, uterine artery embolization and severe pos-partum hemorrhage. Given previous medical history, two years after birth a routine transvaginal ultrasound was performed which showed nonspecific, multiple, highly vascularized solid nodules in the uterus, peritoneum and rectus abdominis, confirmed by Magnetic Resonance Imaging. The nodules were surgically removed and diagnosed as multifocal PEComa with positive expression for estrogen receptors. The disease progressed with pulmonary metastasis and it was decided to start systemic therapy with Tamoxifen (20 mg daily). During the following two-year close surveillance, the patient was clinically and imagiologicaly stable, without disease progression. PEComas are very unusual tumors and the differential diagnosis include fibroids. In estrogen receptor positive tumors, Tamoxifen may be considered as a therapeutic option.

Keywords: Perivascular epithelioid cell neoplasms; muscle, smooth; myoma; tamoxifen

Perivascular epithelioid cell tumor (PEComa) is part of a rare family of mesenchymal tumors. PEComas occur at multiple sites and can undergo metastasis, recurrence, and aggressive clinical courses. The lung is a common metastatic site of PEComas. The role of estrogen in PEComas is unclear. In humans, estrogen might stimulate PEComa tumour cells because of a mutation in the *TSC2* tumour suppressor gene, through MEK pathway.[1] Blocking estrogen receptors might therefore inactivate the MEK pathway and provide a rationale for therapeutic efficacy.[1] There are few reports about uterine malignant PEComa tumours with pulmonary metastases and fewer about the use of hormonal therapy, including tamoxifen.[1-5] We report a case of a malignant peritoneal PEComa with pulmonary metastasis which has been treated for 2 years with tamoxifen and to the date the patient is alive and well, with a controlled disease.

CASE REPORT

We present a case report of a 35-year-old woman, with no relevant medical or family history. She had previous myomectomies at the age of 21 and 23 due to abnormal uterine hemorrhage, refractory to medical therapy, followed by uterine artery embolization at 27 years old. At 28, during a cesarean section, it was performed a myomectomy due to severe hemor-

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rhage from a 15 cm myoma, with subsequent hemorrhagic shock, transfusion support and admission to the intensive care unit. Histological analysis revealed a subserous leiomyoma with areas of stromal decidualization. Moreover, during cesarean section, multiple small lesions suggestive of deciduosis were also observed. Two years after delivery, she remained asymptomatic in terms of uterine hemorrhage. However, given her history of uterine fibroids, her general general practitioner requested a pelvic ultrasound. This exam revealed a 26x16 mm posterior uterine nodule and a solid formation measuring 35x27 mm with central vascularization located in the left supra-annexal region. This last lesion was found in the thickness of the left anterior rectus abdominis, by computerized tomography (CT). Magnetic resonance imaging (MRI) confirmed a nonspecific, solid nodularity and revealed no pathognomonic characteristics of endometriomas, aggressiveness or locoregional invasion. She maintained regular gynecological vigilance, and 2 years later, ultrasound and MRI showed a dimensional increase of multiple solid lesions. These lesions presented as highly vascularized with a single branched vessel dispersed throughout the peritoneal cavity (Douglas pouch, superior wall bladder, next to left ovary, posterior to rectus abdominis, inferior to right ovary) (Figure 1).

Pelvic splenosis, endometriosis or fibroids were the main diagnostic hypotheses. The patient denied a history of abdominal trauma and the abdominal ultrasound did not reveal any splenic alterations. Given the age of the patient and absence of suspicion for malignant disease, no other imaging exams, including CT Thorax, were performed. Due to increase in the size of the lesions and doubts regarding the diagnosis, she was submitted to excision of nodules in the peritoneal cavity, of the mesosigmoid, and myomectomy of a subserous nodule (Figure 2).

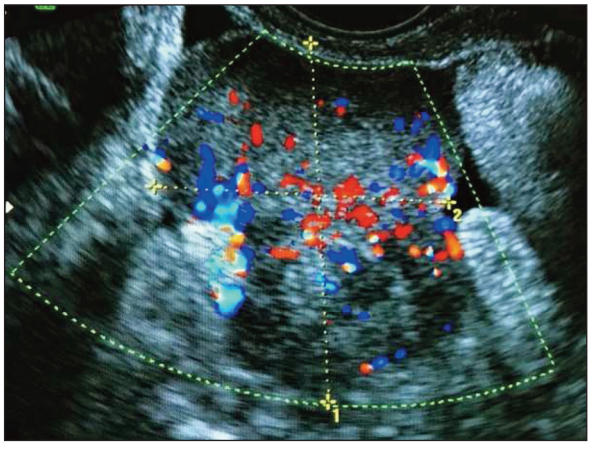

FIGURE 1: Ultrasound image of the highly vascularized peritoneal nodules.

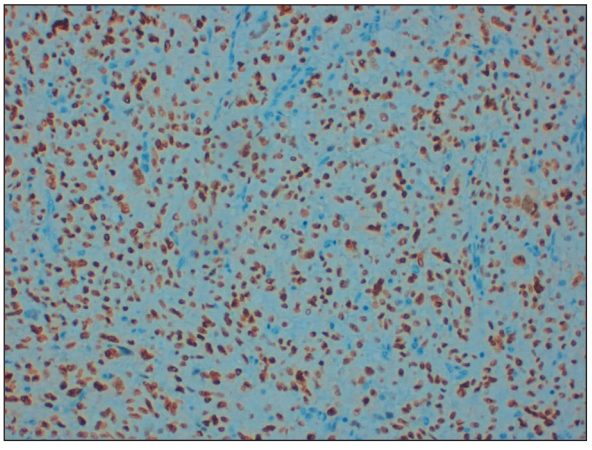

FIGURE 2: Tumor cell expression for estrogen receptors (immunostaining, x200).

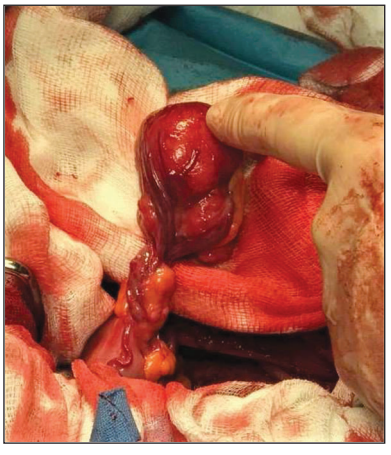

FIGURE 3: Intraoperative image of a highly vascularized mesosigmoid nodule with 3 cm of diameter.

Histology showed that some nodules had mild atypia and low mitotic activity (1 mitosis in 2 mm^2), while others were poorly delimited and were comprised of fusocellular or epithelioid cells, with vast, eosinophilic cytoplasm and moderate to severe nuclear atypia, with 2-3 mitoses per 2 mm^2. Neoplastic cells presented strong and diffuse expression of smooth muscle actin, desmin, caldesmon, HMB45 and estrogen receptors, and were negative for cytokeratins (AE1/AE3 and CAM5.2), CD34, DOG1,

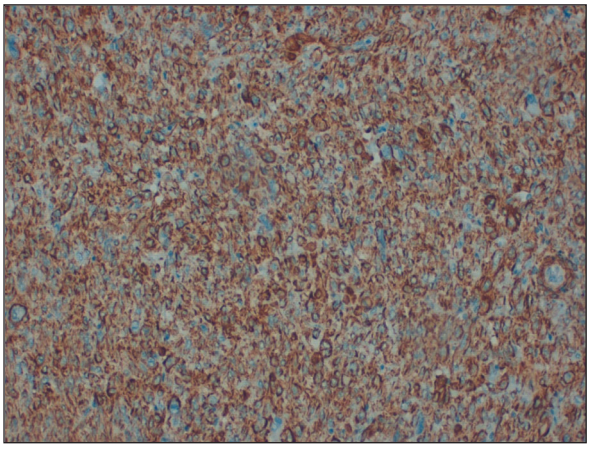

FIGURE 4: Neoplastic cells with strong and diffuse expression for caldesmon (Immunostaining, 200x).

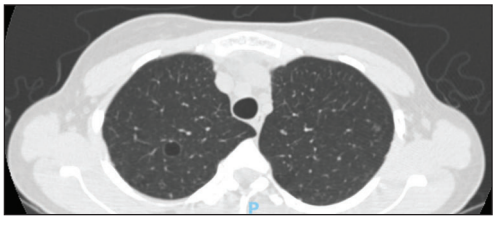

FIGURE 5: Cavitated pulmonary metastasis in the right upper lobe seen on chest computerized tomography.

CD117, S100, MyoD1 and myogenin (Figure 3 and Figure 4). The initial histological diagnosis was probable leiomyosarcoma. Notwithstanding, a reassessment of the histological results was performed. Such reassessment confirmed the hypothesis of multifocal PEComa, part of peritoneal pecomatosis, with some high-risk morphological characteristics.

Post-surgery positron emission tomography (PET) revealed 2 pelvic nodular lesions suspicious for malignancy or inflammatory alterations and multiple non-fixing bilateral pulmonary nodules, mostly infracentimetric. A further CT exam found these lesions suggestive of cavitated metastatic lesions (Figure 5).

Adenopathies were not seen in any of the aforementioned exams. A CT-guided biopsy showed pulmonary metastasis of a spindle cell neoplasia consistent with the hypothesis of pecomatosis/leiomyosarcoma (1 mitosis/2 mm^2 Ki67-2%, no necrosis; expression of estrogen receptors in 50% of tumor cells). The patient was referred to a specialized center in sarcoma treatment where after a multidisciplinary evaluation, systemic therapy with Tamoxifen (20 mg daily) (Farmoz, Tecnimede - Sociedade Tecnico-medicinal, S.A., Portugal) was initiated, prior previous authorization. Verbal consent was obtained from the patient, after the scarce treatment options for this rare disease were presented, as the benefits and disadvantages of each treatment. She maintains the therapy with tolerance and high compliance. Molecular tests of the *TSC1* and *TSC2* genes were not performed as the patient did not meet clinical diagnostic criteria or suspicion of having tuberous sclerosis. In the last 2 years, the disease has remained stable, with 2 contrast-enhanced nodules in the Douglas pouch and no lesions with increased metabolism detected in PET-CT.

Written informed consent was obtained from the included patient, and the patient agreed to publish the details of her case and any accompanying pathological images. The hospital ethics committee (n º 92/2020) approved this study and the publication of the case's details.

DISCUSSION

PEComas include a wide range of lesions such as angiomyolipomas, clear cell "sugar" tumors, or lymphangioleiomyomatosis (LAM) tumors.[6] It is a tumor originating from perivascular epithelioid cells, with 25 to 40% of reported cases of gynecological origin, making differential diagnosis with fibroids. Case reports have been described affecting multiple organs such as pancreas, small intestine, colon, mesentery, lung, kidney, large ligament, vulva, heart, bladder, breast, skull base, soft tissue, and prostate.[7] Most cases occur in women and the mean age of onset is 54 years.[6] These tumors can be associated with mutations or deletions in mechanistic target of rapamycin (mTOR) suppressor genes -*TSC1* or *TSC2*-related to tuberous sclerosis.[8] PEComas form nests and/or layers of epithelioid-like cells and spindle cells with clear or eosinophilic granular cytoplasm.[6] They are variably positive for smooth muscle (desmin-most common, h-caldesmon, smooth muscle actin) and melanocytic (HMB45-most common and melan-A markers).[9] Radical surgical excision and mTOR inhibitors (e.g. temsirolimus) are therapeutic options, as these tumors are characterized by high resistance

to radiation and chemotherapy.[10-12] In pulmonary LAM, several reports have described the successful use of hormone manipulation with a variety of modalities such as tamoxifen, oophorectomy, or luteinizing hormone–releasing hormone analogs.[13-15] There are some reports of late pulmonary metastasis in malignant uterine PEComa, in some cases manifested as multiple cystic, cavity-like lesions treated with surgery or gonadotropin-releasing hormone analogue.[3,4] In this report, we presented the use of tamoxifen as a valid therapeutic choice in a case of PEComa with estrogen receptors expression. To validate the use of Tamoxifen in these particular cases, an extended follow-up time is required. For a correct diagnosis of PEComa, a high diagnostic suspicion and use of immunohistochemical markers is essential, given the need for close surveillance due to the potential for aggressive behavior of PEComas. In tumors with positive estrogen receptors, tamoxifen therapy may be considered.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Inês Margarida Neves Gomes, Cláudia Cristina Reis Vinagre;* ***Design:*** *Inês Margarida Neves Gomes, Cláudia Cristina Reis Vinagre, Jorge Da Cunha Oliveira, Ana Cristina Da Costa Ferreira De Vilhena,* ***Control/Supervision:*** *Inês Margarida Neves Gomes, Cláudia Cristina Reis Vinagre;* ***Data Collection and/or Processing:*** *Inês Margarida Neves Gomes, Inês Calvinho de Oliveira, Pedro Martinho Santos Sequeira, Ana Cristina Da Costa Ferreira De Vilhena, Jorge Da Cunha Oliveira;* ***Analysis and/or Interpretation:*** *Jorge Da Cunha Oliveira, Ana Cristina Da Costa Ferreira De Vilhena;* ***Literature Review:*** *Inês Margarida Neves Gomes, Inês Calvinho de Oliveira;* ***Writing the Article:*** *Inês Margarida Neves Gomes;* ***Critical Review:*** *Pedro Martinho Santos Sequeira, Jorge Da Cunha Oliveira, Ana Cristina Da Costa Ferreira De Vilhena;* ***References and Fundings:*** *Inês Margarida Neves Gomes.*

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