Case 1 – A case of gynecological PEComa

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Abstract
Perivascular epithelioid cell tumors (PEComas) are a heterogeneous group of rare mesenchymal neoplasms composed of epithelioid cells which express melanocytic and myogenic markers, such as HMB-45, desmin and actin. In March 2013, we visited a postmenopausal 51-year-old woman with a suspected diagnosis of uterine PEComa diagnosed by a dilation and curettage of the lining of the uterus. After the histological revision of the formalin-fixed paraffin-embedded (FFPE) material by our expert pathologist, we confirmed the diagnosis and referred the patient for complete primary surgery. On November 2013, the patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with no macroscopically detectable residual cancer. However, in January 2014, due to voiding dysfunction and inconstant vaginal bleeding, the patient underwent magnetic resonance imaging (MRI) which documented multiple irregular lesions in the pelvis suspected as recurrent PEComa. Considering the early relapse of PEComa after optimal primary surgery, we suggested a systemic treatment with the combination of gemcitabine and docetaxel. For logistic reasons, the patients started the chemotherapy in her district hospital. After two cycles of chemotherapy the patient died due to treatment-related complications.

Key words: PEComa, case report, diagnosis, treatment

Introduction

Perivascular epithelioid cell tumors (PEComas) are a heterogeneous group of rare mesenchymal neoplasms [1, 2], including angiomyolipoma (AML), clear cell "sugar" tumor of the lung (CCST), lymphangioleiomyomatosis (LAM), and several unusual visceral, soft tissue, and bone tumors [3-5]. All PEComas are composed by epithelioid cells which expresses melanocytic and myogenic markers, such as HMB-45, desmin and actin [6, 7].
It has been reported in literature both uterine and ovarian PEComas [8-10], however the most common location in the female genital tract is uterus [11].
Here, we report a case of a primary uterine PEComa, with a very aggressive clinical behavior.

Case report

First clinical presentation

In March 2013, a postmenopausal 51-year-old woman was seen at her district hospital after experiencing menorrhagia, without any other symptoms. The patient has a good performance status (Eastern Cooperative Oncology Group [ECOG PS] 0), with a body mass index (BMI) of 20 kg/m^2 and a medical history of hypertension and anxiety. She was the mother of two surviving children and she had in total four pregnancies. No family history for cancer was documented.

According to the local physicians, she started an antihemorrhagic therapy with medroxyprogesterone acetate (MPA) 150 mg once a day. However, due to the non-resolution of the symptom, in August 2013 the patient underwent dilation and curettage (D&C) of the lining of the uterus with a non-conclusive pathologic diagnosis of uterine PEComa versus clear cell carcinoma.
Transvaginal ultrasound scan showed an abnormally increased uterus (82 mm × 11 mm × 10 mm) with an endometrial thickness of 9 mm. Moreover, an irregular, highly vascularized thickening of 39 mm was detected in the central part of the posterior wall of the uterus with a maximum diameter of 39 mm. The ovaries were regular for position and dimensions.
The computed tomography (CT) scan showed that the size of the liver was increased but without any evidence

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of distant metastases. The CT scan confirmed a lesion of approximately 4 cm in the posterior wall of the uterus.
Considering the unclear diagnosis and the rarity of PEComas, she was referred to our referral institution for a second opinion.

Histological revision

We revised, with an expert pathologist in this field in our institution, the formalin-fixed paraffin-embedded (FFPE) material. After hematoxylin-eosin (HE) and immunohistochemical (IHC) stains of several 4-µm sections, positivity for HMB-45, microphthalmia transcription factor and focally for desmin was detected. Cytokeratins and actin were negative.
Overall, the diagnosis of malignant PEComa was confirmed and the patient was referred for complete primary surgery.

Primary surgery and follow up

On November 2013, the patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with no macroscopically detectable residual cancer. No surgery complications were reported and a regular follow up visit every three months was planned. However, in January 2014 the patient accessed our Institution reporting voiding dysfunction and inconstant vaginal bleeding. At gynecological evaluation, a 3 cm lesion was detected in the upper part of vagina.
A magnetic resonance imaging (MRI) was performed with the evidence of multiple irregular lesions in the pelvis: one closed to the caudal part of the bladder, which incorporated the urethra, another in correspondence of the anterior wall of the vagina and a third infiltrating the sigma. Moreover, pathologic bilateral abdominal lymph nodes were detected along the iliac axes and in the para-aortic area.
Considering the early relapse of PEComa after optimal primary surgery, the best treatment option was the timely start of a systemic chemotherapy with the combination of gemcitabine 900 mg/m^2 on days 1 and 8 and docetaxel 100 mg/m^2 on days 1 every 3 weeks [12-14]. Moreover, we suggested a second treatment options with mammalian target of rapamycin (mTOR) inhibitors in case of chemotherapy failure [15-17].
For logistic reasons, the patient chose to receive chemotherapy at her district hospital. Unfortunately, after two cycles of chemotherapy she died due to treatment-related complications.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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Commentary

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors characterized by histologically and immunohistochemically distinctive perivascular epithelioid cells as defined by the WHO (World Health Organization) [1]. The term perivascular epithelioid cell (PEC) for these cells was coined by Bonetti et al., in 1992, when the presence of this specific cell was proposed as a common pathological characteristic of a series of rare diseases in different anatomical locations [2]. According to this definition, PEComas include different tumors including kidney angiomyolipoma (AML), clear cell sugar tumors (CCST), lung lymphangioleiomyomatosis (LAM) and not otherwise specified PEComa (NOS) [2].

LAM is a cystic lung disease characterized by a progressive infiltration of the lung interstitial by smooth muscle cells. Most of the patients are young women. AMLs are benign tumors, which tend to grow slowly and can undergo follow up to monitor their growth.

PEComa-NOS is a less well-characterized type of PEComa, as the name suggests. CCST is a benign tumor, which can develop in the lung, but some cases are described in skin and urethra too, characterized by epithelioid cells with "water"clear cytoplasm.

PEComas such as LAM or AML are found in patients with tuberous sclerosis (TSC), an autosomal dominant disease characterized by benign tumors growing in the brain and on other vital organs such as the kidneys and heart [2]. TSC is caused by germline mutations in TSC1 or TSC2, which are involved in the genesis of PEComas.

Malignant forms of PEComas that can metastasize can occur, differently from AML and LAM. PEComa-NOS have been described in a range of diverse anatomic locations including the breast, pancreas, colon, and heart. However, the female genitourinary tract, in particular the uterus, is one of the most common primary sites for PEComa-NOS [3]. Clinical outcomes vary widely in patients with PEComa-NOS of the uterus [3].

There are limited data regarding risk factors for the development of these tumors, epidemiologic patterns of disease or natural history following initial treatment. Most of our knowledge comes from case reports and case series. A strong female predominance has consistently been reported, most likely accounted for by the high proportion of cases originating from the female genitourinary tract. Even though a diagnosis of PEComa-NOS typically occurs in middle age, PEComa-NOS has been reported in patients ranging from 3 to 97 years of age [4].

The biologic behavior of PEComas is unpredictable; some tumors are unresectable or they present metastases at the time of diagnosis [5], but most of them present as benign disease, apparently curable with surgical resection alone. Furthermore, some of them relapse after surgery, in some cases many years postoperatively, in other cases the behavior is very aggressive, as in the case here presented.

In PEComas of almost every anatomic site, the principal therapy remains surgery, when possible. Surgical resection in patients with oligometastatic disease has demonstrated benefit, with improvement in disease-free intervals in many cases of relapsed disease, especially in late relapses [5]. Radiation therapy, utilized in both the neoadjuvant and adjuvant setting, did not show convincing results [5]. In addition, chemotherapy showed very few confirmed responses [6].

A new approach in the advanced setting is represented by targeted therapy, in particular mTOR inhibition. PEComas and PEComa-NOS frequently express mutations in the TSC1 and/or TSC2 genes, which regulate cell proliferation via the mTOR pathway [7], leading to the use of mTOR inhibitors in the clinical setting for metastatic or recurrent disease. This new pharmacological approach resulted in significant clinical activity in patients with PEComa, although the evidence for efficacy comes from case reports and case series. This therapy showed a partial response of disease with reduction of tumoral burden as demonstrated in patients with AML and LAM [8].
In conclusion, PEComas are a rare disease with different behavior and few treatment options and for which additional investigation is needed.

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