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Case Report Open Access

A Lymphatically Metastasized Perivascular Epithelioid Cell Tumor from the Uterus

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Abstract

Perivascular Epithelioid tumor (PEComa) is a rare malignancy which may occur at various anatomic sites. A case is described of PEComa in multiple lymph nodes in a 34 year old woman with adenocarcinoma of the cervix. Laparoscopic pelvic lymph node dissection revealed perivascular epithelioid tumor cells in 15/34 pelvic lymph nodes and no sign of the adenocarcinoma. At subsequent radical hysterectomy the primary tumor was found in the uterus, besides the stage IB1 adenocarcinoma of the cervix. No adjuvant treatment was given and the patient remained well, until the time of evaluation, 20 months after diagnosis.

A systematic review is performed about gynecological PEComa with lymphatic involvement concerning diagnosis, treatment and overall survival.

Keywords: Cervical cancer; Lymph node; Metastasis; PEComa; Treatment; Systematic review; Survival

Introduction

In 1992 the concept of perivascular epithelioid cells was described by Bonetti et al [1]. Zamboni et al. first published a case of 'PEComa' in the literature in 1996 and hitherto 321 papers on this topic have been published (09/10/13) [2]. The WHO has defined the PEComa as a tumor of mesenchymal origin and stated that PEComas displaying any combination of infiltrative growth, marked hypercellularity, nuclear enlargement and hyperchromasia, high mitotic activity, atypical mitotic figures, and coagulative necrosis should be regarded as malignant [3]. The description of the biological behavior differs widely in literature; some cases developed metastasis, local recurrence and died of disease [4]. The patient presented in the following case had a rare double tumor involving PEComa.

Case

A 34 year old woman, Para 0, presenting with irregular vaginal bleeding was diagnosed with early stage adenocarcinoma of the cervix and referred to our hospital for fertility-sparing treatment. She had no other symptoms and no history of other disease. Cervical cytology four years earlier had been normal. She did not smoke, use medication, alcohol or drugs. There was no known allergy. Her family history provided no added information. No case of tuberous sclerosis complex was known in her relatives. At colposcopy the squamo-columnar junction was not visible due to a lesion with enhanced and atypical vascularization in all four quadrants. In addition a polyp-like structure of 1.5 cm in diameter was removed, revealing a moderately differentiated adenocarcinoma at histopathological examination. Bimanual examination showed a firm cervix with no evidence of parametrial infiltration. At MR imaging, a tumor measuring 3.1×2.5×1.6 cm located within the cervix was visualized. A parailiacal lymph node was seen and measured 4.5 mm in short axis direction. This lymph node was unsuspicious. It was concluded that this was a FIGO (International Federation of Gynecology and Obstetrics) stage IB1 moderately differentiated adenocarcinoma of the cervix measuring >2 cm.

Standard treatment would involve radical hysterectomy with pelvic lymph node dissection. This patient, however, opted for fertility-sparing treatment. Fertility-sparing surgery has been shown to be safe for tumors measuring <2 cm without lymph node involvement [5]. Because of the unfavorable prognostic factors (i.e. adenocarcinoma and tumor size measured by MRI >2 cm) present in this patient a step-by-step approach for tailored treatment was proposed: a robot-assisted laparoscopic pelvic lymph node dissection should exclude lymph node involvement, and in case no metastases would be found neo-adjuvant chemotherapy should down-stage the tumor to allow a vaginal radical trachelectomy. At the laparoscopic pelvic lymph node dissection no metastases of adenocarcinoma were found, but perivascular epithelioid tumor cells were seen in 15/34 pelvic lymph nodes. We concluded that these cells should be regarded as metastases of PEComa, a second primary tumor.

Subsequently, a PET scan was made to detect the primary tumor and other distant metastases of the PEComa. This scan only revealed, besides the cervical tumor a parasternal hotspot caused by a benign atheroma cyst (Figure 1). It is known that, at least in middle-aged women, about 40% of the PEComas arise in the gynecological tract [6]. Therefore, it was decided to perform a radical hysterectomy to a) treat the cervical cancer probably without the need for adjuvant therapy and therefore not compromising further PEComa treatment if needed, b) possibly find the primary PEComa. Histological examination showed a well differentiated adenocarcinoma of the cervix measuring 1.5 cm in horizontal direction with an infiltrative depth of 7 mm (Figure 2a). Furthermore a 1.2 cm focus of PEComa with angioinvasive growth was found in the uterus (Figure 2b). At the time of radical hysterectomy also a precaval lymph node, more proximal than previously sampled, again showed a focus of PEComa (Figure 2c). These findings suggest

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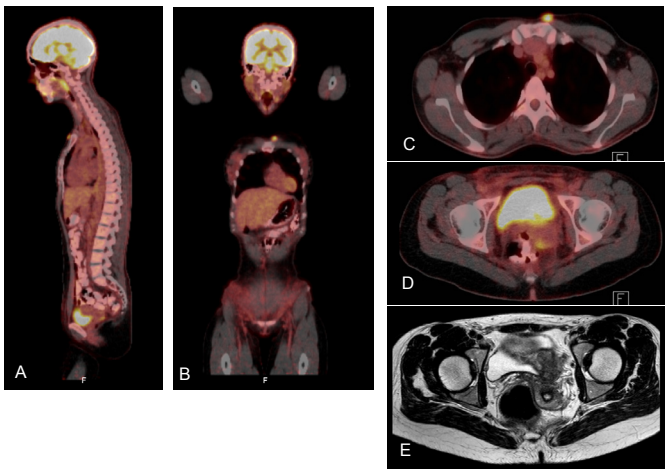

Figure 1: A PET/CT scan of the 34-year old patient 3 weeks after the robot-assisted pelvic lymphadenectomy. A parasternal hotspot appeared to be a atheroma cyst. The pelvic lesion was thought to represent the adenocarcinoma of the cervix or the PEComa.

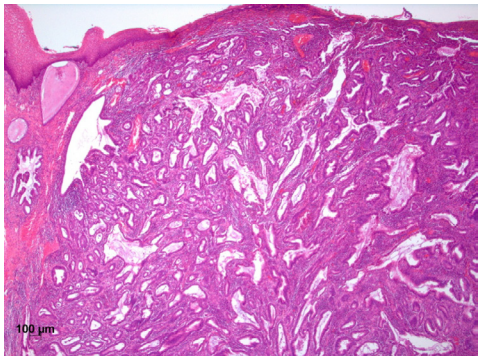

Figure 2a: Well differentiated adenocarcninoma of the cervix, measuring 1.5cm in horizontal direction with an infiltrative depth of 7mm.

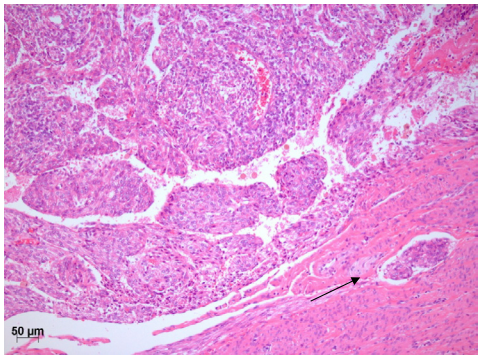

Figure 2b: Malignant PEComa of the uterus including vascular space invasion (arrow).

that besides the well differentiated adenocarcinoma of the cervix FIGO stage IBI <2 cm, for which she was optimal treated; this patient also had a lymphatically metastasized primary PEComa of the uterus. No adjuvant treatment was started in the absence of clinical, biochemical, or radiological evaluable disease. Over 18 months after treatment, the patient is still without evidence of disease at CT and clinical follow-up.

Discussion

PEComa has been identified at multiple anatomic sites, such as liver, vulva, rectum, heart, breast, urinary bladder, abdominal wall and pancreas [6]. It has been associated with very little (if any) symptoms, though abdominal pain and bleeding have been reported. Radiologically, PEComas can appear very homogeneous, resembling small, benign smooth muscle lesions. PET/CT can be used for primary diagnosis and follow-up [7,8]. Two studies present cases in whom disseminated disease as well as response to treatment were monitored using FDG-PET. However, in our case PET/CT failed to detect the (small) precaval lymph node metastasis and was therefore not used in follow-up.

Zekry et al. have published a systematic review on all (n=26) reported gynecological PEComa cases [4]. In their series only two cases of uterine corpus PEComa lymphatic metastases were present, similar to our patient. These two young women (9 and 18 years) were described by Jeon and Lee [9] and Darai et al. [10]. The 9-year old patient was treated with hysterectomy, lymphadenectomy, chemotherapy and radiation therapy and had no evidence of disease at 18 month follow-up. The 18-year old patient was treated with local excision only and was alive with evidence op disease at 24 months follow-up. We found another three cases of uterine PEComa with nodal involvement (Table 1), none of whom received adjuvant treatment after surgical removal and survived [11,12]. In addition, one other case concerning a double tumor involving the uterus was published [13]. This patient presented with uterine bleeding and was diagnosed with a well-differentiated adenocarcinoma of the endometrium with bilateral ovarian involvement and a uterine PEComa. No lymphadenopathy was found. This PEComa showed no mitotic figures or necrosis and malignant behavior of this particular PEComa is therefore unlikely.

We performed a systematic literature search to find all PEComa cases with lymph node involvement. The results are presented in Table 1. Patients with lymphatic metastasized PEComa have been treated very inconsistently, but in most patients the primary tumor was surgically removed. The choice of adjuvant therapy includes chemoradiation, radiotherapy, and no adjuvant treatment without obvious differences in overall survival. Only recently limited clinical studies have reported encouraging responses after mTOR inhibitor treatment [14]. Perivascular epithelioid cells can be found in a number of related neoplasms, such as Lymphangioleiomyomatosis (LAM) and Angiomyolipoma (AML), which are related to the genetic alterations of Tuberous Sclerosis Complex (TSC). TSC is caused by mutations in the TSC1/TSC2 genes, which are responsible for inhibition of the Rheb/

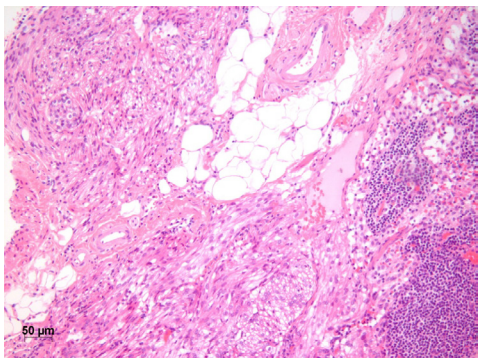

Figure 2c: Malignant PEComa found in the sampling biopsy of the precaval lymph node.

Author	Sex, age	Origin	LNM	Treatment	Adjuvant treatment	Follow-up
Cui et al. [19]	Male, 47 yrs	Kidney	Multiple paraortal LNM	Nephrectomy and LND	No	No evidence of disease, 2 yrs FU
Liu et al. [20]	Female , 33 yrs	Uterus	Multiple LNM	Neoadjuvant chemotherapy (type unknown), debulking	Chemotherapy (type unknown),	No evidence of disease, 8 months FU
Bonis et al. [21]	Female, 39 yrs	Pelvis	Multiple paraortal LNM	Tumor excision left pelvic and paraortal LND	No	No evidence of disease, 1 yr FU
Huang et al. [22]	Female, 78 yrs	Kidney	Regional LNM	Radical nephrectomy	No	Died of disseminated disease (lungs and bones) 5 months postoperatively
Chen et al. [23]	Female, 16 yrs	Pelvis	Enlarged pelvic, mesocolon, iliac LNM	Debulking and pelvic floor LND	Chemotherapy (type unknown),	Recurrence 2 months after debulking
Harris et al. [24]	Male, 87 yrs	Knee	Recurrence -1/8 Inguinal LNM and pulmonary metastases	Primary debulking	Groin LND	Alive with disease 40 months FU
Bonetti et al. [25]	1. Female, 28 yrs	Serosa ileum	Mesenteric LNM	Tumour resection	No	Died 28 months after surgery because of liver insufficiency due to hepatic metastases
	2. Female, 19 yrs	Uterus	1 month after surgery pelvic LNM	Hysterectomy – 1 month later pelvic LND and inguinal LND	Adriamycin, ifosfamide, radiotherapy	10 months after chemotherapy: local recurrence, lung and bone metastases, died 18 months after surgery
Daraï et al. [10]	Female, 18 yrs	Corpus uteri	Recurrence - Pelvic LNM	Excision		Alive with disease 24 months
Ryan et al. [26]	Female, 15 yrs	Rectum	Mesenteric LNM	Low anterior resection	Doxorubicin, ifosfamide	No evidence of disease 9 months FU
Liang et al. [11]	Female, 59 yrs	Corpus uteri	3/13 pelvic and para-aortal LNM: proliferation of benign smooth muscle bundles (LLM)	Radical hysterectomy, BSO pelvic LND, paraortal LND, omentectomy, appendectomy	None	No information
Calder et al. [27]		Unknown primary	Cervical LNM	Excision	No	5 yrs FU scalp nodule→ excision. Hereafter no information.
Vang et al. [12]	1. Female, 49 yrs	Corpus uteri	Pelvic LLM	Radical hysterectomy, BSO	No	No evidence of disease, 4.5 yrs FU
	2. Female, 58 yrs	Corpus uteri and endometrial cancer	Pelvic LLM	Radical hysterectomy, BSO	No	Lost to follow-up
Jeon et al. [9]	Female, 9 yrs	Corpus uteri	1 pelvic, paraortal and precaval LNM	2 cycles neo-adjuvant chemotherapy with vincristine/ ifosfamide/ doxorubincin (VID), hysterectomy and pelvic LND	6x VID regimen, radiotherapy 45 Gray	No evidence of disease 1.5 yrs FU, at 2 yrs FU the patient developed acute lymphoblastic leukaemia, treated and in the maintenance phase [28]

LNM: lymph node metastases
LND: lymph node dissection
FU: follow-up
BSO: bilateral salpingoophorectomy
LLM: lymphangioleiomyomatosis = pecomatosis

Table 1: Systematic literature search involving all PEComa cases with lymphatic metastases.

mTOR/p70S6K pathway. It has been proven that mTOR activation is also common to sporadic, non-TSC-related AMLs and PEComas [14-16]. This suggests that mTOR inhibitors may be of therapeutic use in this disease. Clearly, no randomized controlled-trials or preclinical studies have been performed concerning this rare disease. No literature was found on mTOR-inhibitors in the treatment of lymphadenopathy in PEComa. In addition, none of the overviews contained sufficient numbers to study variables predicting prognosis. The patient presented in this report had no signs of tuberous sclerosis complex.

Only a very small minority (9%) of PEComas are tuberous sclerosis complex- associated [6]. Survival rates are difficult to provide. PEComa has a very heterogeneous presentation with an unpredictable clinical outcome. A certain selection bias of reported cases and studies cannot be excluded. Folpe et al. [6] summarizes 61 PEComas previously reported in English literature. Follow-up data was available in 45 cases (74%). Local recurrences and metastases were noted in 3 (7%) and 9 (20%) of patients. At the time of follow-up, 35 patients (78%) were alive without evidence of disease, 5 were alive with recurrent or metastatic disease (11%) and 4 patients were dead of disease (9%). Zekry et al. reports survival of 53 gynecological PEComas if they provided any clinical or pathological follow-up data [4]. In 9 patients; the outcome was not specified. In the remaining 44 patients (83%), 6 (14%) were dead of disease. Our review on lymphatically metastasized PEComa (Table 1) showed dead of disease in 3/13 patients (23%) and alive with disease in also 3 patients.

Also, there are a few reports on 'PEComatosis': the term for tumor multicentricity or propensity for multiple tumor development [17,18]. Fadare et al. [17] describe a 41-years old patient with a 7 cm large cervical PEComa with several intraabdominal aggregates of PEComa cells in the myometrium, ovaries, small bowel lamina propria, and ovarian hilus. They describe these aggregates as 'PEComatosis', since morphologic features and immunophenotype between the cervical and extracervical lesions are similar. Either these lesions arise from the same primary site or progenitor or they represent tissue response to the same stimulus such as tuberous sclerosis. After surgical excision of these aggregates no evidence of recurrence or metastasis was present at 29 months of follow-up. We are not sure how to interpret the lymphatic disseminated PEComa in our patient. Although disseminated disease is

clearly a feature of malignant behavior, histological examination of the tumor did not reveal signs of aggressive disease, i.e. nucleair atypia, mitotic activity, or necrosis. But there was a breakthrough the lymph node capsule by the PEComa tumor. Also, PEComatosis involving lymph nodes has hitherto not been described.

In conclusion, uterine PEComa is a rare malignancy with variable presentation and inconsistent treatment protocols. Lymphatic involvement is common and sometimes treated with anthracycline and/or vincaloid based chemotherapy and/or radiation therapy, without obvious improvement of prognosis. Genetic studies support encouraging results of mTOR inhibitors. Prognosis is generally good; however death of disease has been reported. Until now death only occurred in other patients than with uterine PEComa and lymph node involvement.

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