A Lymphatically Metastasized Perivascular Epithelioid Cell Tumor from the Uterus

Klerkx WM1 *, Sie-Go DMDS2, Daan NMP1, Witteveen PO1 and Verheijen RHM1

1Department of Gynaecology and Obstetrics, University Medical Center Utrecht, Netherlands
2Department of Pathology, University Medical Center Utrecht, The Netherlands
3Department of Medical Oncology, University Medical Center Utrecht, Netherlands

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 squamocolumnar junction was not visible due to a lesion with enhanced and complex was known in her relatives. At colposcopy the squamoco-

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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 of 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/
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 lymphadenoapthy 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. Felpke 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%). Zecky 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 unknown primary cervical PEComa with several intraabdominal aggregates of PEComa. 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 dissemination of 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. nuclear 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 vincadil 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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References
