

A very rare case of uterine PEComa HMB45 negative: primitive or relapse?

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ABSTRACT

Perivascular epithelioid cell tumors (PEComas) represent a rare group of tumours with uncertain malignancy potential exhibiting an immunophenotype characterized by actin and Human Melanoma Black 45 (HMB45) immunoreactivity.

Our case concerns about a rare malignant uterine perivascular epithelioid cell tumour diagnosed in a patient underwent to subtotal hysterectomy with unclear diagnosis, 12 years before. Histological diagnosis after colposcopic exam with biopsy revealed a perivascular epithelioid cell tumor, with immunohistochemical profile negative for HMB45. Negativity for HMB45, already described in literature, could be due to important cellular modifications of tumoral tissue.

In our case, tumour was unresectable, progression of disease occurred during medical treatment and the patient died after 6 months. Lack of information about first surgery doesn't allow to surely categorize the tumor as primitive or relapse.

Further studies are necessary to understand some immunohistochemical anomaly like negativity for HMB45.

Keywords: immunohistochemistry; PEComa; primitive; rare tumors; relapse.

INTRODUCTION

Perivascular epithelioid cell tumors (PEComas) represent a rare group of tumours with unpredictable malignancy potential. The term "PEComa" was originally coined by Zamboni et al. In 1992⁽¹⁾ and it is the current nomenclature for tumors composed of pecs, other than angiomyolipoma (AML), clear cell myomelanocytic tumor of the falciiform/ligamentum teres (CCMT), clear cell sugar tumor of the lung (CCST), lymphangioliomyomatosis (LAM) and clear cell tumors of the pancreas, rectum, peritoneum, uterus, vagina, thigh and heart⁽²⁾. The recent literature has paid respectable attention to tumors exhibiting an immunophenotype consistent with a perivascular epithelioid cell (PEC) differentiation characterized by actin and Human Melanoma Black 45 (HMB45) immunoreactivity⁽³⁾. Our case is a very rare uterine PEComa negative for HMB45.

SOMMARIO

I tumori a cellule epitelioidi perivascolari (PEComa) rappresentano un gruppo raro di neoplasie che esibiscono un immunofenotipo caratterizzato da actina ed Human Melanoma Black 45 (HMB45). Il nostro caso clinico riguarda un raro tumore a cellule epitelioidi perivascolari maligno dell'utero diagnosticato in una paziente sottoposta a isterectomia subtotale con esame istologico dubbio, 12 anni prima. La diagnosi istologica dopo colposcopia con biopsia è stata di tumore a cellule epitelioidi perivascolari, con profilo immunostochimico negativo per HMB45. La negatività per HMB45, già descritta in letteratura, potrebbe essere dovuta a importanti modificazioni cellulari del tessuto tumorale. Nel nostro caso, la neoplasia era inoperabile, si è verificata progressione di malattia durante il trattamento chemioterapico e la paziente è deceduta dopo 6 mesi. La mancanza di informazioni riguardo il primo intervento chirurgico non consente di diagnosticare con certezza la neoplasia come primitiva o come recidiva. Successivi studi sono necessari per comprendere alcune anomalie immunoistochimiche come la negatività per HMB45.

CASE PRESENTATION

Our case report concerns about a 54-year-old romanian parous female, with negative clinical history for non-gynecologic disease or surgery. The patient was underwent in 1996 to subtotal hysterectomy and bilateral salpingo-oophorectomy in Romania with histological evidence of uterine corpus tumoral lesion, without specific histological diagnosis. The patient was admitted to our hospital in 2012 July for abdominal pain and genital bleeding. Computed tomography (CT) findings highlighted an oval mass measuring 90x65 mm with origin from Douglas pouch between bladder and rectum, inhomogeneous density with hypodense center; positive left iliac and obturator nodes, aortic carrefour and right inguinal nodes. Magnetic resonance imaging (MRI) revealed a necrotic hypodense solid mass of vaginal vault measuring about 65x70 mm, with high cellularity and highly vascularized tissue (MRI T2-weighted, **Figure 1**). Positron emission tomography (PET) scan revealed a considerable accumulation of radiotracer in the pelvic region, especially in the

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Figure 1.
MRI T2-weighted imaging: pelvic oval mass, inhomogeneous density with hypodense center.

previous localization of uterus, with positive left iliac lymph nodes. Pap smear highlighted numerous squamous metaplastic and atypical epithelioid cells. Colposcopy revealed a large, hard and bleeding mass (8 cm) which involved the entire vaginal vault. A colposcopically directed biopsy of the mass was performed and histological examination revealed a malignant mesenchymal neoplasm based on epithelioid cells displaying large granular eosinophilic cytoplasm, round vesicular nucleus and prominent nucleoli; pleomorphic multi-nucleated cells, neoplastic alveolar-like distribution pattern cells and tumor necrosis with high mitotic index ($> 1 \times 50$ high power fields HPF). Immunohistochemical pattern was positive for desmin, S-100, actin 1A, epithelial membrane antigen (EMA), microphthalmia transcription factor (MITF), cytokeratin AE1/AE3 (CKAE1/AE3) and Melan-A, instead immunohistochemically negative for myogenin and HMB45. **Figures 2 and 3** show particular

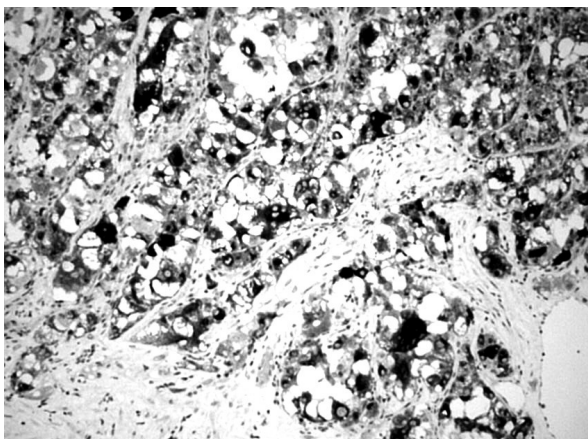


Figure 2.
Tumour shows widespread and high reactivity for melan-A.

histologic features of tumour.

In consideration of the above, pathologists made diagnosis of malignant PEComa.

During hospital stay hepatitis B was diagnosed and antiretroviral therapy was started. In consideration of unresectable tumour, multidisciplinary team including gynecologic oncologist, medical oncologist, radiotherapist and pathologist, proposed palliative chemotherapy with gemcitabine 800 mg/m² (total dose 1200 mg), every 21 days for 3 courses, between October to December 2012. CT and MRI imaging performed during treatment revealed progression of disease, so the team proposed home support therapy. The patient died after 6 months in Romania.

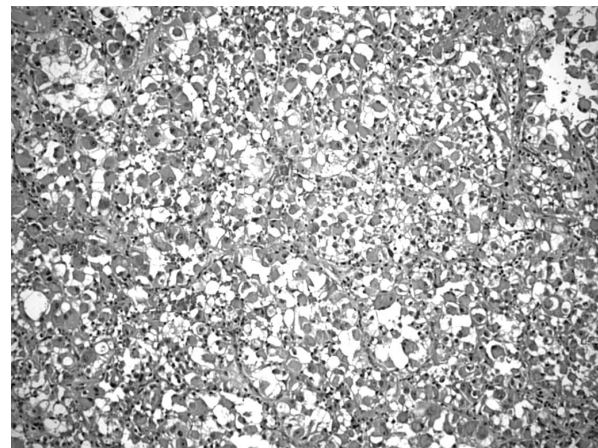


Figure 3.
Epithelioid cells displaying large granular eosinophilic cytoplasm with rhabdoid morphology. Eccentric nucleus and prominent nucleoli.

DISCUSSION

It is known that the prevalent sites of PEComa are the gastrointestinal tract, genitourinary tract and retroperitoneum, but uterus is the most commonly reported site of involvement of PEComa (accounting for about 40% of reported cases). In this report we described a case of unusual epithelioid tumor of uterus, 12 years after of unclear diagnosis of uterine neoplasm.

The issue about origin of tumour was evaluated. In consideration of the particular site of lesion, we considered differential diagnosis between soft tissue and uterus PEComas. Also if many informations about first surgery were not available, we know that the patient was underwent to a subtotal hysterectomy.

In fact, we think that colposcopic directed biopsy was performed to a mass originated from transformation of the cervix and probably also from a small part of uterine corpus left inside the pelvis.

It's known that differential diagnosis of soft tissue and gynecologic PEComas is predominantly guided by the location of the tumor, as well as by its morphology⁽⁴⁾. In consideration of both elements this tumour would be diagnosed as uterine PEComa.

PEComa represents a very heterogeneous group of neoplasm, with many types of cellular and immunohistochemical patterns. Vang and Kempson⁽⁵⁾ described eight examples of PEComa distinguishing a morphologic variety of neoplasms including tumors with a tongue-like growth pattern composed of sheets of HMB45-positive clear epithelioid cells, which they called group A, to circumscribed tumors composed of hyalinized stroma and neoplastic cells focally positive for HMB45 and extensively immunoreactive for actin and desmin, which they referred to as group B.

Epithelioid cells with eosinophilic to clear cytoplasm and positive immunostaining for both melanocytic and myoid differentiation are distinctive features of PEComas⁽⁶⁾. Histological examination of our tumor revealed epithelioid cells displaying with large granular eosinophilic cytoplasm, round vesicular nucleus and prominent nucleoli, and dual expression of melanocytic and myoid markers.

Among rarer uterine tumours, leiomyosarcoma is the most common subtype of uterine sarcoma. Often, clinical features of PEComas are the same of leiomyosarcoma, including abnormal vaginal bleeding, palpable pelvic mass and pelvic pain. Histological diagnosis of leiomyosarcoma can be difficult since many smooth muscle tumor of the uterus show hypercellularity, severe nuclear atypia and high mitotic rate. Sometimes differential diagnosis between PEComas and leiomyosarcomas is simplified by immunohistochemistry and molecular biology, because the latter express only smooth muscle markers such as desmin, caldesmon, actin and histone deacetylase.

In our case, the uterine PEComa can't be exactly categorized by Vang and Kempson classification, because, as described above, immunohistochemical study revealed no reactivity for HMB45, but histological diagnosis was supported by presence of both melanocytic and muscular elements. In fact, all PEComas display dual expression of melanocytic (HMB-45, Melan A, NKIC3, MITF, tyrosinase) and smooth muscle (actin, desmin, caldesmon, calponin) markers⁽⁶⁾. However, high immunoreaction for actin and desmin supports classification in the

group B by Vang and Kempson.

Folpe and colleagues⁽⁴⁾ recently reviewed 61 cases of PEC-oma, which 100% were HMB-45 positive, 59% were smooth muscle actin positive, 41% were Melan-A positive, 33% were CD117 positive, 31% were desmin positive, 11% were S-100 positive, and 0% was cytokeratin positive.

Immunohistochemical pattern represents a very important tool for diagnosis of PEComa but it's not sufficient to determine the final diagnosis because there are different patterns, models are heterogeneous and results can be various. Our case report requested specific analysis for differential diagnosis of PEComa with other muscular neoplasms, because, as described above, immunohistochemical evaluation didn't highlight the usual positivity for HMB45. The case herein presented showed strong and diffuse staining for both Melan-A and MITF, two melanocytic markers, which is not an usual finding in other tumors like sarcomas. Moreover, immunohistochemical reactivity for Melan-A and actin was significant for diagnosis of PEComa while negativity for HMB45, already described in literature⁽⁷⁾, could be due to important cellular modifications of tumoral tissue. About this, a very interesting theory is that PEComa originates from transformation of a smooth muscular cells tumour. In fact Silva et al.⁽⁸⁾ described a case of leiomyosarcoma in which primitive tumour was negative for HMB45 while after 7 years metastatic tumour was reactive for HMB45 and pathologists diagnosed it as perivascular epithelioid cells malignant tumour. In our case, in consideration of the lack of information about first diagnosis, presumable theory could be that previous tumor was a misdiagnosed PEC-oma but we cannot be totally definitive about this.

The optimal treatment for this group of tumour is not well established but surgery seems to be the gold standard for primitive PEComas and metastatic ones, with purpose to obtain adequate resection margins⁽⁹⁾. Treatment for locally advanced and metastatic tumour are different, including surgery, chemotherapy and radiotherapy. Recent literature⁽¹⁰⁾ has highlighted the efficacy of mammalian target of rapamycin (mTOR) inhibitors in the patients affected from malignant PEComas but there is not sure evidence yet about the gold standard chemotherapy of PEComas and further studies are necessary to demonstrate the optimal treatment. We used gemcitabine for palliative treatment accounting the unavailability of recent described target therapies.

In our case, analysis and study of the patient was difficult for absence of clinical information about first diagnosis and surgical treatment performed in Romania. In fact, we speculate about difficult and inadequate first surgical treatment, but description of surgery and specific histological diagnosis are not available. The patient was admitted to our hospital with a big mass invading pelvic organs as bowel and bladder, low performance status, resulting in unresectable tumour. In consideration of entire clinical history, we can surely categorize the neoplasm as a malignant tumor, but it's known that there are specific features to analytically determine the malignancy potential.

Biological behavior of PEComas is difficult to define⁽²⁾. Folpe and colleagues⁽⁴⁾ proposed that the disease could be classified into three subgroups, including the benign, uncertain malignant potential, and malignant. These criteria for malignancy are: size of >8.0 cm, mitotic count of >1 per 50 HPF and necrosis, with benign, uncertain malignant potential and malignant categories based on the presence of none, 1 or ≥2 of these three criteria, respectively. The benign tumor has no alarming features (e.g. Diameter

of the tumor ≤5 cm, non-infiltrative, non-high nuclear grade and cellularity, mitotic rate ≤1x50 HPF), while uncertain malignant potential tumor shows pleomorphous or multinucleated giant cells only, or sized over 5 cm in diameter only. In this regard size of tumour (over 5 cm in diameter) and high mitotic rate are two important indicator of relapse. In our case, lack of information about surgery doesn't allow to surely categorized our tumor as primitive PEComa or relapse of this. If presented tumor is a primitive PEComa, size and mitotic rate index establish that our uterine PEC-oma is a malignant tumour by classification described, with high percentage of relapse. Again, it's known that relapse is itself an important indicator of malignancy. So, in consideration of both theories, we classified the tumour as a malignant PEComa.

In conclusion, PEComas are rare uncertain malignancy tumors. Diagnosis is based on microscopic histology and immunohistochemical pattern while prognosis is influenced by biological behavior and stage of disease at the time of diagnosis. Further studies are necessary to understand some immunohistochemical anomaly like negativity for HMB45, also if it's a rare event.

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