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Case Report
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UTERINE PERIVASCULAR EPITHELIOID CELL TUMOR DIAGNOSTIC DIFFERENCES BETWEEN ENDOMETRIAL CURETTAGE MATERIAL AND RESECTION MATERIAL AND HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL APPROACH TO THE DIFFICULTIES IN DIFFERENTIAL DIAGNOSIS

Büşra ERŞAN ERDEM[1]*, Havva ERDEM[1]

[1]*Ordu University, Training and Research Hospital, Department of Pathology, 52200, Ordu, Turkey*

Abstract: Uterine perivascular epithelioid cell tumor is a rare mesenchymal tumor consisting of histologically and immunohistochemically distinctive perivascular epithelioid cells. These tumors' being rare, having different morphological features and having similar immunohistochemical expression findings to that of some tumors lead to diagnostic difficulties and misdiagnoses. In the present case report, we aimed to discuss the traps we fell into while diagnosing the curettage material as neuroendocrine tumor and how we have been directed to the diagnosis of perivascular epithelioid cell tumor, as well as to discuss what to be taken into account while making the differential diagnosis under the guidance of the literature.

Keywords: PEComa, Perivascular epithelioid cell tumors, Uterus, Neuroendocrine tumor, Endometrial polyp

***Corresponding author:** Ordu University, Training and Research Hospital, Department of Pathology, 52200, Ordu, Turkey
E mail: busraersanerdem@gmail.com (B. ERŞAN ERDEM)
Büşra ERŞAN ERDEM https://orcid.org/0000-0003-1464-6673
Havva ERDEM https://orcid.org/0000-0002-3074-0240

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1. Introduction

Perivascular epithelioid cell tumor (PEComa) is a family of mesenchymal tumors that characteristically co-express melanocytic and myoid markers. PEComas can be seen in many different anatomic localizations. The uterus is the second most common location after retroperitoneum. To date, less than 100 cases of uterine PEComa have been reported in the literature (Bennet et al., 2018). As they are rarely encountered, they may not be considered at the first step particularly in the tissues such as curettage material. Different morphological subtypes of the tumor and confusing findings in the immunohistochemical expressions are the factors enhancing the risk of misdiagnosis. In the present case, CD56 ve Synaptophysin expression in the curettage material has led us to make the diagnosis of neuroendocrine tumor (NET), thus caused misdiagnosis. However, the diagnosis of PEComa could have been made after detailed evaluation of the results of histomorphologic and immunohistochemical examination of the hysterectomy material.

2. Case Presentation

A 48-year-old female patient had vaginal bleeding for 17 days. Based on the endometrial thickness of 16 mm measured on US examination, diagnostic curettage was performed. Microscopic examination revealed disordered proliferative endometrium and tumoral infiltration with nested patern in the hyalinized stroma (Figure 1a and 1b). Tumoral infiltration had no connection with the endometrial tissue and was usually in the form of divergent tissue samples. The sections demonstrated cellular infiltration with the cells having clear-eosinophilic cytoplasm, round nucleus, thin-dispersed chromatin like salt- and pepper, focally pronounced nucleolus, and ambiguous nuclear atypia. These cells established nests in a hyalinized stroma and contained crush artifacts. No mitosis or necrosis was seen. Immunohistochemical examination demonstrated strong positive expression with CD56 (Figure 1c), focal positivity with synaptophysin (Figure 1d) and focal dot-like staining pattern with pancytokeratin, Actin, CD117, and CD10 were negative. Ki-67 proliferation index was low. The case was diagnosed with low-grade NET based on the morphologic and immunohistochemical findings. Because the tumoral groups on microscopic examination were separate from the endometrial tissue, the clinician was informed about the probability of NET of the cervix, and resection was recommended accordingly.

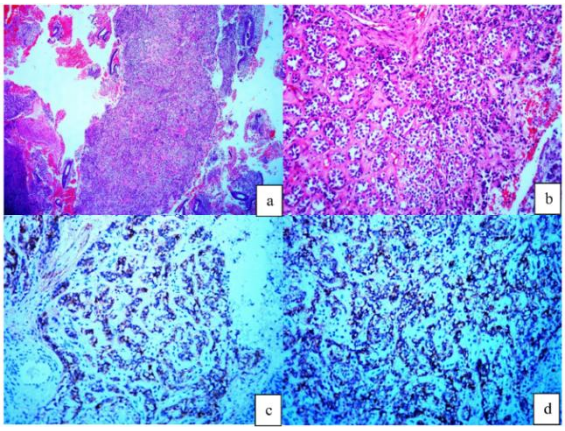

Figure 1. a) In the curretage specimen, tumoral infiltration in endometrial tissue (Hematoxylin and Eosinx40); b) Nested patern of tumor (Hematoxylin and Eosinx200); c) Positive expression with CD56 (Immunohistochemistryx100); d) Positive expression with Synaptophysin (Immunohistochemistryx200).

Three weeks later, the patient underwent hysterectomy. Macroscopic examination revealed a polypoid lesion of 4x2x1.3 cm localized in the uterine fundus. On the microscopic examination of the polyp, there were cells with eosinophilic cytoplasm and round nucleus forming islands, nests, trabecules and cords in the hyalinized stroma, as well as fusiform cells forming fascicules and focal pseudoglandular and giant cell morphology (Figure 2a, 2b, 2c, 2d). In addition to the vascular structures with a thick wall in many areas of the tumor, there were also cleft/slit like vascular structures in focal areas.

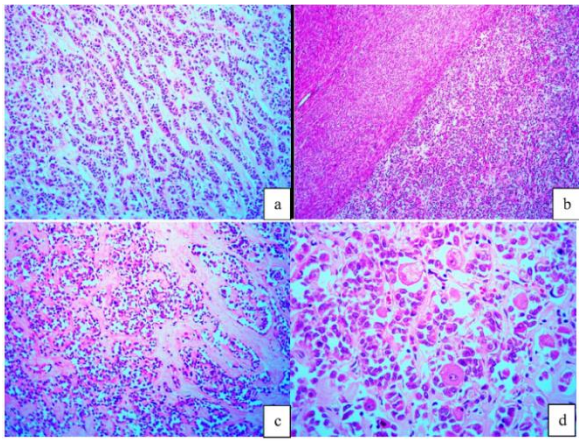

Figure 2. a) The tumor was observed in many different patterns in the hysterectomy specimen like trabecular pattern (Hematoxylin and Eosinx200); b) Spindle (left) and epiteloid(right) morphology (Hematoxylin and Eosinx200); c) Cords and nests in the hyalinized stroma (Hematoxylin and Eosinx200); d) Tumor cells have eosinophilic cytoplasm and round nucleus, focally mononuclear giant cell with large cytoplasm are observed (Hematoxylin and Eosinx400).

Besides, endometrial stroma infiltration was detected in this tumor, which had infiltrative margins (Figure 3a). Tongue-like infiltration of the tumor to the myometrium resembled Endometrial Stromal Sarcoma (ESS) (Figure 3b).

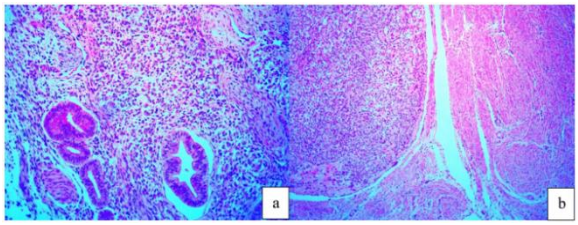

Figure 3. a) Endometrial stroma infiltration (Hematoxylin and Eosinx200); b) Tongue-like infiltration of the tumor to the myometrium resembled Endometrial Stromal Sarcoma(Hematoxylin and Eosinx100).

Different morphological patterns in the tumor resulted in diagnostic diversity. Immunohistochemical evaluations revealed strong expression with Vimentin, ER, PR, CD56, Actin (Figure 4a), Desmin (Figure 4b), Beta-catenin and HMB-45 (Figure 4c) in the tumor cells. Positivity was observed with synaptophysin, scattered expression with pancytokeratin, and focal expression with Melan-a (Figure 4d).

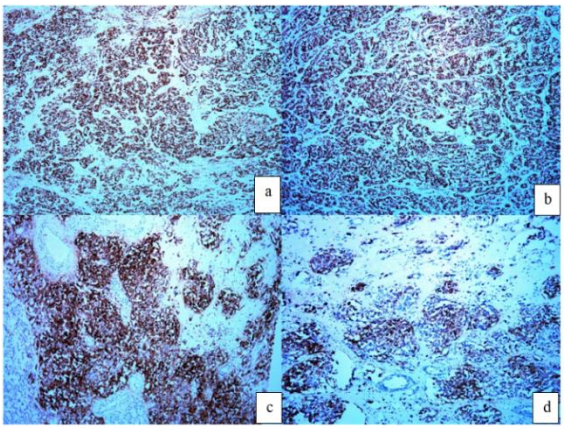

Figure 4. Tumor characteristically co-express melanocytic and myoid markers: a) Actin (Immunohistochemistryx100); b) Desmin (Immunohistochemistryx100); c) HMB45 (Immunohistochemistryx200); d) Melan-a (Immunohistochemistryx100).

No reaction was detected with CD10, Calretinin, CD117, DOG1, bcl-1, NSE and Chromogranin. Differential diagnosis included ESS, low grade neuroendocrine tumors (NET), Gastrointestinal stromal tumor (GIST), PEcoma and smooth muscle tumors (SMTs). In addition to expression of HMB-45 and Melan-a, NSE and chromogranin negativity despite CD56 and synaptophysin positivity eliminated NET. CD10, CD117 and bcl-1 negativity allowed discrimination from ESS. Epithelioid-type malignant SMTs were included in the differential diagnosis due to SMA positivity and

epithelioid morphology, but the absence of mitosis, necrosis and cellular atypia eliminated this diagnosis. GISTs were also excluded because CD117 and DOG1 positivity seen in GISTs was not detected in the present case. Thus, the case was diagnosed with perivascular epithelioid cell tumor (PEComa) based on the immunohistochemical expressions and morphologic features.

3. Discussion

PEComas are uncommon tumours, described initially by Bonetti et al. (1992). The World Health Organization defines PEComas as "mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells" (Oliva et al., 2014). This family of tumors includes angiomyolipoma (AML), clear cell sugar tumor of the lung (CCST), lymphangioleiomyomatosis (LAM), and group of rare, morphologically and immunophenotypically similar lesions arising at a variety of visceral and soft tissue sites (Hornick and Fletcher, 2006).

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder characterized by the growth of benign tumors in multiple organs including the brain, kidney, heart, liver and skin. While there is a strong relationship between AML and LAM and TSC, this relationship is weaker in other members of the PEComa family (Folpe and Kwiatkowski, 2010). Our case was sporadic and not associated with TSC.

The uterus in particular is the second most commonly involved site following retroperitoneum. However, there are less than 100 PEComa cases including the study of 41 cases reported by Fadare (Fadare, 2008), which is the largest case series in the literature (Bennett et al., 2018). PEComas are usually located as myometrial or subserosal nodular or multinodular lesions (Fadare, 2008). However, rarely the uterine PEComas can present as polypoid lesions mimicking an endometrial polyp (Wang at al., 2018). In the present case as well, we did not think of PEComa at the first stage as the lesion looked like an endometrial polyp.

Under microscopic examination, PEComas can display a wide range of morphological variations. Typically, they are composed of nests and sheets usually of epithelioid but occasionally of spindled cells with clear to granular eosinophilic cytoplasm and a focal association with blood vessel walls (Hornick and Fletcher, 2006). It was reported that even papillary structures and pseudoglandular morphology can be seen in addition to dominant epithelioid morphology (Fadare, 2008). Hyalinized stroma is another morphological variation seen widely, and such type of cases are called as sclerosing PEComas (Folpe and Kwiatkowski, 2010). Bizarre mononuclear and multinuclear giant cells and pronounced macronucleolus with melanin pigment resembling melanoma can be seen as well (Bennett, 2018). In addition to the thin, delicate capillary-like vascular structure in the PEcomas, vessels with thick walls are frequently seen in the periphery of the tumor. Besides, sometimes presence of slit/cleft-like vascular structures morphologically resembles the LAM.

The pattern of invasion into surrounding tissues is multiple; destructively infiltrative growth, pushing border and permeative pattern- tonguee like infiltration that seen in ESS.

HMB45 is the most sensitive melanocytic marker of PEComas followed closely by Melan-a. Co-expression of melanocytic markers and smooth muscle actin is considered as the hallmark of the PEComas. Positivity of S100 has been reported as 30% in the literatüre (Fadare, 2008). Positive expression with desmin, SMA and h-Caldesmon is frequently encountered. Pancytokeratin expression as well can be seen with a unique case reported in the literature (Folpe et al., 2005). Although there are cases showing NSE and CD56 expression in the literature, no chromogranin or synoptophysin positivity has been reported (Zahang et al., 2017; Hong et al., 2018). Uterine PEComas include hormone receptors, CD10, CD1a, CD117, MUM1, and vimentin (Ferenczi et al., 2012; Wang et al., 2018).

In the present case, histologically the tumor makes island and nest structures in the hyalinized stroma. Due to the morphological pattern and the absence of nuclear atypia, necrosis and mitosis, the most likely diagnosis is low grade NETs. The expression of CD56 and synaptophysin supported the diagnosis of NET. It has been reported in the literature that CD56 positivity can also be seen in PEComas (Zhang et al., 2017). However, synaptophysin positivity has never been reported in the literature until now. Therefore, our case is important in terms of showing that synaptophysin expression can be seen in PEComas.

The original PEComa classification developed by Folpe et al. categorized tumors as either benign, uncertain malignant potential or malignant. Benign is defined as displaying no atypical features: gross size<5 cm, non-infiltrative, non-high nuclear grade and cellularity, mitotic rate ≤1/50HPF, no necrosis, no vascular invasion. Tumors of uncertain malignant potential are defined as having nuclear pleomorphism or/multinucleated giant cells or gross size >5 cm. The malignant category is defined as having 2 or more concerning features: gross size>5 cm, infiltrative growth, high-grade nuclear features, necrosis, vascular invasion, or a mitotic rate >1/50 HPF (Folpe et al., 2005).

Uterine PEComas are included in the differential diagnosis of many tumors due to their histomorphologic and immunohistochemical features. Firstly, uterine SMTs come to the mind primarily because of localizations and shared morphological and immunohistochemical features. Especially, epithelioid SMTs grow in nests, cords or diffuse sheets and are composed predominately of epithelioid cells with clear-to-eosinophilic cytoplasm and contain thick-walled blood vessels like PEComa. SMTs typically lack the delicate capillary network seen in many PEComas. The presence of multinucleated giant

cells and ''spider cell''-like cells may also be a clue to the diagnosis of PEComa. Uterine SMTs express smooth muscle markers and can be HMB45-positive like PEComa (Baker and Oliva, 2007). In the literature, it has been reported that CD1a is positive in PEComas but negative in uterine smooth muscle tumors (Fadare and Liang, 2008). Morphological (pseudoglandular morphology, slit-like and delicate vascular structures) and immunohistochemical features (HMB45, Melan-a and CD1a positivity) made a diagnosis in favor of PEComa in our case.

Low grade NETs are also included in the differential diagnosis because of epithelioid morphology, nested pattern, and minimal nuclear atypia. As in our case, in limited specimens such as curettage, histopathological examination showing a limited area and immuno-expression supportive of NET may lead to misdiagnosis. The nested pattern, absence of remarkable nuclear atypia and mitosis, and CD56 and synaptophysin expression in the present case have led us to make the diagnosis of low-grade NET. In the literature, CD56 positivity was reported in the PEcomas (Zhang et al., 2017). Therefore, in order to avoid the possibility of misdiagnosis, actin and HMB45 should be included in the profile, and detailed histopathological examination should be performed keeping the morphological variations of PEComa in mind.

ESSs are the other differential diagnosis. Although ESS and PEComas have similar histomorphologic features, certain features such as predominant nested pattern and perivascular radial lining are not seen in ESSs. Tongue-like infiltration can be seen in ESSs and PEcomas. ESS may be positive for smooth-muscle markers and PEComas may be positive for CD10 (Baker and Oliva, 2007). As well as the studies showing that ESSs do not express HMB45 or Melan-a, there are studies reporting that focal positivity can be seen by 2-23.5% with HMB45 (Baker and Oliva, 2007; Albores-Saavedra et al., 2014). In the literature, it was reported that bcl-1 expression is specific to ESS but not expected in PEComas (Lee and et al., 2012). In the light of these informations, nested pattern, diffuse expression with HMB45, Melan-a and CD10, bcl-1 negativity in the present case were all considered in favor of PEComa.

Gastrointestinal stromal tumors (GIST) may also enter the differential diagnosis of PEComas.

While CD117 expression can be observed in PEComas, CD34 is negative.

Epithelioid PEComas may be confused with carcinomas such as clear cell carcinoma. Although rare PEComas may show focal cytokeratin expression, they do not show the diffuse cytokeratin expression seen in clear cell carcinomas. Therefore, the presence of melanocytic marker expression is very valuable in distinguishing PEComa from carcinoma.

Melanoma can be distinguished from PEComa. Expression of S100, HMB45 and Melan-a can be seen in both. However, S100 positivity is more common in melanomas. Therefore, it is important to evaluate the morphology and expression of actin, desmin and h-caldesmon.

PEComa can be distinguished from paraganglioma. pPEComa is negative for chromogranin A and synaptophysin. Additionally paraganglioma shows more organoid growth.

In conclusion, the factors that increase the risk of misdiagnosis in PEComas are: their rarity, different histomorphological pattern structure and common immunohistochemical expression characteristics. HMB45, Melan-a, smooth muscle markers positivity and detailed histopathological examination, are the most valuable features in diagnosis of PEComa.

Author Contributions

All authors have equal contribution. All authors reviewed and approved the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical Approval/Informed Consent

Necessary information was given to the family and an informed consent form was obtained.

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