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Moderately Differentiated Neuroendocrine Cell Carcinoma of the Vulva: A Case Report and Review of the Literature

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Abstract

Primary vulvar neuroendocrine carcinoma are extremely rare. There have been few cases of these tumors most of which have been considered as Merkel cell carcinoma. This report describes a moderately differentiated neuroendocrine cell carcinoma that was not compatible to any of previously reported cases. The patient underwent left hemivulvectomy and bilateral inguinal lymph node dissection. Pathology examination revealed a 5×5 cm mass with no lymph node involvement. Post—op evaluation ruled out any regional and distant metastasis and thereby did not receive chemotherapy or radiotherapy. Four years of close follow up evidenced no signs of recurrence, regional involvement or distant metastasis.

Keywords

Epithelial tumor; Neuroendocrine cell; Vulva; Vulvectomy

Introduction

Neuroendocrine neoplasms can arise in any organ throughout the body. A wide spectrum of neuroendocrine tumors and tumors with neuroendocrine attributes has been identified throughout the female genital tract. However, vulva is considered an extremely uncommon primary site for developing these tumors, with only few cases reported in medical literature (1).

Herein, we report a rare case of moderately differentiated malignant epithelial tumor with neuroendocrine features in the vulva which represents a distinct subset of clinical, morphological and immunohistochemical manifestations. We will discuss some remarkable features pertaining to medical practice through a review of literature, and will tailor our suggestions.

Case Report

A 44 year—old female, gravid3, para 3 was presented with a mass in her vulva since about one year ago, enlarging in the last 3 months while she had no pain or purulent discharge. The patient had neither vaginal bleeding, nor any discharge. Genital examination indicated a 5×5 cm non—tender, firm, mobile mass in left labium major. No palpable lymph node was detected in inguinal region. Speculum exam showed a healthy looking cervix and vagina. Uterus and adnexa seemed normal. Brief systemic examination yielded no further positive findings.

Based on these preliminary findings, an excisional biopsy was scheduled. Subsequent pathological examination suggested the diagnosis of malignant epithelial tumor with neuroendocrine features. It too indicated that the margins were involved by tumor. The patient underwent left hemivulvectomy after which frozen samples negated the involvement of tumor margins. To detect whether or not the inguinal region was harboring the micrometastatic cells, bilateral inguinal lymph node operation was performed dissecting 18 lymph nodes to assure there is no nodal involvement.

In histopathological examination, the tumor composed of sheets of proliferating large epithelial tumor cells, possessing scanty eosinophilic cytoplasm and nuclei with coarse chromatin. Tumor cells were arranged as trabeculae, ribbons and nests. There were mitotic figures and microscopic necrotic foci were also present (Figure 1). Lymph nodes of inguinal region were free of tumor.

Immuno histochemical staining depicted strong positive reaction for Neuron—Specific Enolase (NSE),
Synoptophysin, and weak positive reaction for Chromogranin and HMW keratin. Stains for CK20, CK7, Melan-A and GCDFP–15 were nonreactive (Figure 2). Our histological and immuno histochemical findings were consistent with moderately differentiated malignant epithelial tumor with neuroendocrine feature.

Postoperative work-up, including octreotide scan and thoraco–abdominal spiral CT scan showed no evidence of nodal involvement or distant metastasis. Given these clinicopathological findings we did not include the administration of postoperative chemotherapy or radiotherapy in her treatment protocol. The patient remained healthy and is still alive with no evidence of recurrence, locoregional involvement, or distant metastasis after four year of follow–up.

Discussion

Neuroendocrine tumors represent a large class of cancers that can occur anywhere throughout the body. They exhibit a wide variety of morphological and clinical features. Literally, neuroendocrine carcinoma take their names from the cells they developed from or from the regions where they first appear (e.g. small–cell lung cancer, paraganglioma, and Merkel cell carcinoma) (2). However, contemporary classification of neuroendocrine tumors use the distribution pattern of intermediate filaments such as neurofilament and cytokeratins the criteria for grouping them into two general subtypes of ‘epithelial’ and ‘neural’. Epithelial–originated tumors are in turn sub–classified by means of cellular differentiation into well–, moderately–, and poorly– differentiated carcinomas (3). Immuno histochemical staining for three neuroendocrine markers including Chromogranin, Synaptophysin and Neuron–Specific Enolase are commonly undertaken for the diagnosis of neuroendocrine tumors (4). In placing the current case, our findings showed readily detectable malignant large epithelial cells, virtually all of which exhibited moderate differentiation and displayed neuroendocrine attributes.

Vulvar primary neuroendocrine cell tumor is an extremely rare tumor with less than twenty cases of Merkel Cell Carcinoma (MCC) and a single case of neuroendocrine carcinoma with paraganglioma features reported in the literature (6,15). The clinicopathological features of these cases (including the presented case) are summarized in Table 1. The current case is presumed to be the first one reporting a moderately differentiated malignant large epithelial cell tumor with neuroendocrine features arising in vulva.

The origin of primary vulvar neuroendocrine cell tumors has not been fully elucidated yet (1). Merkel cell is proposed as a potential cell of origin of epithelial neuroendocrine. Accordingly, Merkel cell carcinoma (MCC) is the only vulvar neuroendocrine tumor of epithelial origin that has been presented in the literature so far (17). MCCs have been demonstrated to comprise of cells of varying sizes. On that basis, MCCs are subdivided into three cytohistologically recognizable groups; Intermediate–cell type constitutes the majority of MCC tumors. This variant shows large, solid nodules made of diffuse sheets of basophilic cells with the characteristic round to oval nuclei, powdery chromatin, and inconspicuous nucleoli. The second group is the small cell variant which has small round cells with scant cytoplasm, oval hyperchromatic nuclei, and prominent nucleoli. The tumor cells form solid sheets or clusters, often with crush artifact and nuclear molding. The third group is the least common trabecular variant which has round cells with scant cytoplasm, oval hyperchromatic nuclei, and prominent nucleoli. The tumor cells form solid sheets or clusters, often with crush artifact and nuclear molding. The third group is the least common trabecular variant which has round to polygonal cell shape with abundant cytoplasm; round, centrally located vesicular nuclei; and inconspicuous nucleoli arranged in an organoid, trabecular, or ribbon–like patterns (7). Like any neuroendocrine tumors, MCCs express a range of bio–molecular markers. More specifically, paranuclear, dot–like labeling of keratin intermediate filaments by antibodies to cytokeratin 20 (CK20) has turned out to be an
Neuroendocrine Carcinoma of Vulva, S. Aminimoghaddam, et. al.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Size and site</th>
<th>Treatment</th>
<th>Recurrence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheikh et al. [2]</td>
<td>MCC</td>
<td>63</td>
<td>7*5 cm L lab majus</td>
<td>Wide excision, bilateral inguinal lymphadenectomy, Rad vulvectomy.</td>
<td>8 months, local and distant metastasis</td>
<td>Died before adjuvant therapy, Died at 11 months from pulmonary embolism</td>
</tr>
<tr>
<td>Mohit et al. [3]</td>
<td>MCC</td>
<td>50</td>
<td>10*12 cm L lab majus</td>
<td></td>
<td></td>
<td>Died at 2 years, no</td>
</tr>
<tr>
<td>Pawar et al. [4]</td>
<td>MCC</td>
<td>35</td>
<td>6*4 cm L lab majus</td>
<td>Local excision</td>
<td>No follow-up; tumor in inguinal nodes at examination</td>
<td>Lost for follow-up</td>
</tr>
<tr>
<td>Hierro et al. [5]</td>
<td>MCC</td>
<td>79</td>
<td>7*9 cm R lab majus</td>
<td>Wide local excision</td>
<td>13 months, free of disease</td>
<td>Died at 11 years, postop, myocardial infarction</td>
</tr>
<tr>
<td>Gil Moreno et al. [6]</td>
<td>MCC</td>
<td>74</td>
<td>1.5 cm L lab minus</td>
<td>Wide excision</td>
<td>2 years, inguinal lymph node Rx; 3 months later met autopsy neck node</td>
<td>Died at 2 years, no</td>
</tr>
<tr>
<td>Tang et al. [7]</td>
<td>MCC</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td>Died at 11 days, postop, lymphadenectomy, liver, pulmonary vessels at autopsy</td>
</tr>
<tr>
<td>Bottles et al. [8]</td>
<td>MCC</td>
<td>73</td>
<td>3 cm L lab majus</td>
<td>Rad vulvectomy, L inguinal lymphadenectomy</td>
<td></td>
<td>Died at 13.5 months</td>
</tr>
<tr>
<td>Copeland et al. [9]</td>
<td>MCC</td>
<td>59</td>
<td>8 cm L lab minus</td>
<td>L hemivulvectomy, lymphadenectomy, postop Rx</td>
<td>8 months 2.5 cm rec L, clots, pulmonary mets</td>
<td>Died after third course cheino, autopsy, node, lung, liver, pancreas mets</td>
</tr>
<tr>
<td>Husseinzadeh et al. [10]</td>
<td>MCC</td>
<td>47</td>
<td>4 cm R lab minus</td>
<td>Rad vulvectomy, bilat femoral lymphadenectomy, postop Rx</td>
<td>3 months, R thigh, forehead, probable lung mets-chemo</td>
<td>Died at 17 months</td>
</tr>
<tr>
<td>Chandeying et al. [11]</td>
<td>MCC</td>
<td>28</td>
<td>4 cm R lab majus</td>
<td>Rad vulvectomy, bilateral inguinal lymphadenectomy, postop Rx</td>
<td>No follow-up; tumor in inguinal nodes at surgery</td>
<td>Died from liver mets despite chemo</td>
</tr>
<tr>
<td>Waisel et al. [12]</td>
<td>MCC</td>
<td>33</td>
<td>2 cm L minus</td>
<td>Local excision</td>
<td>10 months prior to vulvar tum R inguinal node, then L men post ex. symphysis pubis, 4 months bladder, R inguinal node, peritoneum</td>
<td>Died at 17 months</td>
</tr>
<tr>
<td>Loret de Mola et al. [13]</td>
<td>MCC</td>
<td>28</td>
<td>2 cm L post fourchette</td>
<td>Wide local excision, L inguinal lymphadenectomy</td>
<td>7 months multiple liver mets, chemo</td>
<td>Died at 19 months with multiple abdominal and thoracic mets</td>
</tr>
<tr>
<td>Chen et al. [14]</td>
<td>MCC</td>
<td>68</td>
<td>3 cm paracervical</td>
<td>Local excision</td>
<td>9 months inguinal nodes; 10 months vulva, scalp, bone, liver, para-squamous lymph nodes</td>
<td>Alive at 12 months with multiple abdominal and thoracic mets</td>
</tr>
<tr>
<td>Nueño et al. [15]</td>
<td>NT with paraganglioma-like features</td>
<td>62</td>
<td>2 cm in R labia majus</td>
<td>Rad vulvectomy, postop Rx</td>
<td>19 months, enlargement of the abdominal and mediastinal lymph node enlargement in CT scan</td>
<td>Alive at 19 months with multiple abdominal and thoracic mets</td>
</tr>
<tr>
<td>Scorry et al. [16]</td>
<td>MCC with glandular and squamous differentiation</td>
<td>68</td>
<td>4 cm L lab minus</td>
<td>Rad vulvectomy, bilat groin, and L pelvic lymphadenectomy</td>
<td>2 months para-squamous lymph node chemo, then Rx</td>
<td>Alive at 4 year with no regional or distant metastases</td>
</tr>
<tr>
<td>Aminimoghaddam S et al. [current case]</td>
<td>Moderately differentiated malignant epithelial tumor with neuroendocrine features</td>
<td>44</td>
<td>5 cm L lab majus</td>
<td>L hemivulvectomy, bilateral inguinal lymphadenectomy,</td>
<td>2 months, no local recurrence, no mets was detected in abdominal and chest CT scan</td>
<td>Alive  at 19 months with multiple abdominal and thoracic mets</td>
</tr>
</tbody>
</table>

Note: Lab, labium; Rx, radiotherapy; chemo, chemotherapy; red, radical; R, right; L, left; postop, postoperative; me, metastases; lymphadenectomy; bilat, bilateral.

Table 1: Neuroendocrine Tumor, Clinical Details of Sixteen Reported Cases

integral part of the distinction of MCC from malignancies such as metastatic small cell carcinoma and melanoma. In few cases in which the CK20 is negative, cytokeratin 7 (CK7) comes to the fore and affirms the diagnosis (4, 7). Our cytological and immune histochemical findings, however, met none of the criteria suggested for the diagnosis of MCC. Hence, we could not associate the current case to any of pre-established variants of MCC nor could we propose a new variant of neuroendocrine carcinoma (18). Moreover, our findings were rather in favour of studies arguing how epithelial neuroendocrine tumors appear to originate from a primitive pluripotent stem cell capable of epithelial or neuroendocrine differentiation (2, 18).

Lack of consensual agreement on a distinct therapeutic approach serves the ongoing debate on the best practice for managing patients with neuroendocrine tumors. Tumor excision with wide margins is suggested.
as the pivotal component of almost all the procedures. The need to perform inguinal dissection is dictated by the size of the tumor and the results of the frozen section (9). Most studies have supported the use of sentinel lymph node biopsy (SLNB) for clinically normal groin. The technique is claimed to predict the likelihood of further nodal involvement, the short-term risk of loco-regional recurrence, and the probability of distant recurrence (10, 13). In the context where we were managing this case, the lymphoscintigraphy technique was not available. So bilateral inguinal lymphadenectomy was undertaken to ensure there was no nodal involvement.

Data emerged from studies that focus on treatment of vulvar tumors acknowledge a multimodality approach as optimal practice. Surgery remains the initial treatment in patients with operable disease. Postoperative radiotherapy should be given if two or more nodes are involved, or there is one node with capsular breach. Systemic chemotherapy is generally reserved for recurrence or disseminated disease (9, 16). Our clinicopathological findings corroborated the tumor–free lymph nodes, the non-involved tumor margins and the absence of distant metastases. In keeping with these findings, we doubted any further benefit of additional chemotherapy or radiotherapy for this particular case.

As a final message on this case, we recommend clinicians to take into account the likelihood of unorthodox clinicomorphological features of neuroendocrine tumors since there is mounting evidence that these tumors have a tremendous potential to run a highly aggressive clinical course. We also suggest that treatment strategies be individualised in accordance with the findings of clinicopathological evaluation in each patient. Pertinently, we encourage clinicians to warrant a careful clinical evaluation and to document the negative previous history of neuroendocrine neoplasm before ruling out metastasis and setting the treatment strategy.

References