**Vulvar Melanoma: A Case Report**

Sherif B. Elsherif*, Silvana C. Faria and Priya R. Bhosale

Department of Diagnostic Radiology, The University of Texas at Austin, USA

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**Abstract**

A 62-year-old female presenting with bleeding from a right vulvar lesion with bilateral enlarged inguinal lymph nodes. The lesion was pathologically proven as melanoma with a negative mutational analysis. She was started on neoadjuvant immunotherapy of ipilimumab and nivolumab for 5 months with a good response to treatment. She then underwent surgical debulking of the tumor except for an unresectable right pelvic lesion because of adhesions. The patient later was started on immunotherapy in addition to adjuvant radiotherapy for local control of the tumor.

Vulvar melanoma represents 3-10% of all vulvar neoplasms. It is one of the common locations of mucosal melanoma which has a distinct molecular signature and a worse prognosis compared to cutaneous melanoma. Immunotherapy and molecular therapy have been showing promising results in these patients.

**INTRODUCTION**

Melanoma of the vulva is the second most common type of vulvar malignancy [1]. Malignant melanoma develops from melanocytes with the skin being the most common (90-91%) site of melanoma. However, melanoma can develop also in mucous membranes (1.3%) such as in the nasal cavity, anorectum, vagina, and vulva [1,2]. Vulvar melanoma is biologically aggressive with a high propensity for local and distant recurrence. Annually, 0.2 to 1.4 of every 100,000 women will be diagnosed with vulvar melanoma [3,4].

Affected women are usually in the fifth to seventh decade compared to a younger presentation at cutaneous melanoma [5]. Vulvar melanoma can present as polypoid mass (35%) or asymptomatic pigmented lesion. Similar to other vulvar tumors, vulvar melanomas can be pruritic, painful or bleeding. The clitoral area and the labia major are the most frequent sites (60%) [1,3,5]. Vulvar melanoma can metastasize, usually to regional lymph nodes, lungs, bones, peritoneum, liver, and brain [2,4]. Vulvar melanoma has a bad prognosis.

**CASE PRESENTATION**

A 62-year-old female presenting with a light bleeding from the right external vulvar lesion. Bilateral inguinal lymphadenopathy was observed at physical examination. The vulvar lesion was biopsied with the diagnosis of melanoma. Mutational analysis was negative for CKIT, BRAF, and NRAS and immunohistochemical staining was positive for Programmed cell death Ligand 1 (PD-L1). The patient underwent pelvic magnetic resonance imaging (MRI) and body positron emission tomography/computed tomography (PET/CT) (Figure 1) to assess for the local and distant spread. The images show the vulvar tumor and involvement of the bilateral inguinal, and right external iliac lymph nodes. The patient was started on neoadjuvant immunotherapy ipilimumab and nivolumab.

After completion of 4 cycles, the patient underwent right radical partial vulvectomy, bilateral inguinofemoral lymph node dissection, lysis of adhesions, right salpingo-oophorectomy, and suboptimal tumor debulking. However, the right pelvic lesion couldn’t be resected as it was fixed to the pelvic sidewall. She recovered well after the surgery except for a feeling of pelvic pressure. Final pathology confirmed the diagnosis of a primary vulvar melanoma metastatic to the inguinal lymph nodes with regression and 65% viable tumor in the primary lesion and complete regression of the metastatic nodes except for one node with only 15% viable tumor. The patient was Breslow Stage V (7.3 mm), Pathological American Joint Commission on Cancer (AJCC) 8th edition ypT4b, ypN3b and ypM0, and Federation of Gynecology and Obstetrics (FIGO) stage IIIC.

Given that the resected lymph nodes showed a positive response to immunotherapy, it was decided that the patient should start again on immunotherapy with the use of adjuvant radiotherapy for the local control of the tumor. The patient completed the radiotherapy course with an improvement of clinical symptoms. Monitoring of disease response was obtained.
with serial PET/CT scans with the possibility of an additional future attempt of surgical debulking depending on the positive response to the immunotherapy.

DISCUSSION

Vulvar melanoma representing 3-10% of all vulvar neoplasms [1]. It is classified pathologically, in order of incidence, into mucosal lentigious (27-57%), nodular (22-28%), unclassified (12-16%), amelanotic (6-27%), and superficial spreading (4-56%) (2, 5-7). Ulcer formations, previous local radiation, Human papillomavirus, diabetes mellitus, or immunosuppression are all predisposing factors [6-8].

Vulvar melanoma has a unique mutational signature that renders these tumors a distinct subtype of melanomas. KIT mutations (particularly exon 11) are the most common mutations (15.8-35%) in primary vulvar melanoma, while NRAS (0-27.6%), BRAF (0-9%), and p53 (0-7.6%) mutations are much less common or absent [9-11]. KIT mutations in vulvar melanoma are typically mutually exclusive with BRAF and NRAS mutations so they don’t coexist together. Programmed cell death 1 (PD-1) (77%) and its ligand PD-L1 (54%) are frequently expressed in vulvar melanomas. On the other hand, BRAF and NRAS mutations characterize cutaneous melanoma, being reported in 20-80% and 4-50% of primary skin melanomas, respectively, whereas KIT mutations occur in only 3% of cases [9-12].

KIT mutations activate multiple downstream signaling cascades (Figure 2), including the RAF/MEK/extracellular...
Diagnosis of vulvar melanoma is mainly based on dermoscopy and biopsy [4]. Vulvar melanoma should be differentiated from benign pigmented lesions, as lentigo simplex, vulvar melanosis, melanocytic nevi, and seborrheic keratosis and from malignant lesions as such as vulvar intraepithelial neoplasia, vulvar squamous cell carcinoma and extramammary Paget disease [1,5]. S-100, Melan-A, and HMB-45 are immunohistochemical markers for melanoma cells with S-100 showing the highest sensitivity (97-100%) and Melan-A protein has the highest specificity (95-100%) [13]. Immunohistochemical staining can also be of a special importance in the diagnosis of amelanocytic melanomas [13].

Dermoscopy can help to differentiate vulvar melanoma from vulvar nevi which are characterized by evenly pigmented, ≤ 1 cm, and red to dark colors papules or macules with regular borders; or vulvar melanosis that usually presents by single or multiple, unevenly pigmented, tan to dark macules or patches with irregular border [4].

Similar to cutaneous melanoma, multiple staging systems can be used for vulvar melanoma including Clark’s original staging system for cutaneous melanoma based on five anatomical levels; Breslow’s based on the depth of invasion from the epidermal granular layer to the deepest dermal invasive melanoma cell; Chung’s based on level of histological involvement; FIGO staging based on the tumor size, lymph node and distant metastases; and the 2002 AJCC updated staging system based on tumor thickness, ulceration, nodal status, distant metastasis and serum lactate dehydrogenase (LDH) level [3,14].

Although Breslow thickness is historically reported as the most important prognostic factor for recurrence in early-stage melanoma, such microstaging might not be readily applied to the vulva as it lacks both surface keratin and underlying granular layers and it doesn’t have a well-defined papillary dermis [1,3,14]. However, Seifried and colleagues recommend using Breslow system by measuring the tumor thickness from the mucosal surface to the deepest point of invasion [15]. The FIGO staging is found to be of little prognostic significance in vulvar melanoma compared to other vulvar neoplasia [4,5]. Moxley and colleagues [3], evaluated the different staging systems for vulvar melanoma and they reported that the 2002 AJCC system was associated with a significant survival difference while there was no such difference in Breslow and Clark [3].

Pelvic MRI can help to differentiate between vulvar melanoma and other malignancies as melanoma appears hyperintense on T1-weighted images, hypointense on T2-weighted images, and not suppressed by fat-saturated sequences [4]. Once a vulvar melanoma has been detected, a total-body skin and eye

Figure 2: Schematic of the RAF/MEK/ERK and PI3K/AKT/mTOR pathways involved in the development of vulvar melanoma and the different targeted molecular therapies used.
examination are mandated to exclude other primary sites of the disease [2]. Due to the high tendency of vulvar melanoma for the local and distant spread, a complete set of imaging scans should be obtained for local and distant staging. Pelvic MRI is used to assess local tumor extension. Chest, abdomen, and brain multi detector computed tomography (MDCT) scan or a whole-body PET/CT scan are used for distant staging [4,8]. Serum LDH may be helpful as a marker for assessing the therapeutic response [4].

Early diagnosis of vulvar melanoma especially before nodal spread can improve the survival. Therefore, any suspicious pigmented lesion in the vulva should be biopsied for appropriate diagnosis [5].

Although currently there are no consensus guidelines regarding the management of vulvar melanoma, the localized disease is typically managed surgically with free resection margins ≥ 8 mm, given the poor tumor response to both chemotherapy and radiotherapy [2,3,9]. Wide local excision is preferred over radical surgery nowadays owing to the poor prognosis of the disease and that both procedures have nearly the same survival outcome. Although radical surgery is associated with increased morbidity (lymphedema and secondary disabilities) and doesn’t influence the survival, some practitioners still consider it the only cure given the lack of adjuvant therapy [3]. Similar to cutaneous melanoma, sentinel lymph node dissection has been reported to be effective for the surgical staging of vulvar melanoma without the substantial morbidity of a complete inguinofemoral lymphadenectomy [16,17]. Radiotherapy can be adjunct for advanced patients as a palliative tool [4].

Combined immunochemotherapy, such as Interferon alpha-2b, recombinant high dose interleukin-2, cytotoxic chemotherapy, biochemotherapy or novel targeted immunotherapy, is currently pursued in late-stage disease [17]. There are no trials in the role of novel targeted immunotherapy specific to vulvar melanomas, and only a handful have been included in other melanoma trials [18-23]. Also, few case reports has documented the use of various immunotherapy agents (alone or with chemotherapy) in vulvar melanoma (Table 1) [6,24-28]. In melanoma patients with failed first-line therapy, c-KIT inhibitors (tyrosine kinase inhibitors as imatinib, sorafenib, and dasatinib) and MEK inhibitors (as trametinib) (Figure 2) are showing promising results in patients harboring these specific genetic mutations and might be applied in vulvar melanoma given the high incidence of these mutations in these patients [20,21,25,29]. Due to the low frequency of BRAF and NRAS mutations in vulvar melanoma, these patients might not greatly benefit from BRAF (vemurafenib and dabrafenib) and NRAS (tipifarnib and selaribum) targeted therapies as they do in other melanomas [30].

Recently the US Food and Drug Administration (FDA) approved ipilimumab (a monoclonal antibody that blocks cytotoxic T-lymphocyte– associated protein 4 [CTLA-4]), nivolumab and pembrolizumab (both are checkpoint inhibitors that block PD-1 protein on cells) for late-stage, unresectable melanoma [4,12]. These drugs have significantly improved the outcome in melanoma patients. For instance, patients receiving nivolumab are associated with a progression-free survival as long as 14 months and also Ipilimumab was reported to prolong the median OS of 21.6 months for advanced melanoma patients [18-23]. Also, few case reports has documented the use of various novel targeted immunotherapy specific to vulvar melanomas, pursed in late-stage disease [17]. There are no trials in the role of biochemotherapy or novel targeted immunotherapy, is currently

**Table 1: Number of patients and study end points in case reports of immunotherapy for vulvar melanoma.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of cases</th>
<th>Adjuvant treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>An et al., (24)</td>
<td>2</td>
<td>IL-2 and INF-α + CT (dacarbazine, cisplatin &amp; vincristine)</td>
<td>Survived 30 m with NED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-2 and INF-α + CT (temozolomide)</td>
<td>Survived 10 m, discontinued treatment due to serious myelosuppression related to CT. Now has lung metastasis</td>
</tr>
<tr>
<td>Handolas et al., (25)</td>
<td>2</td>
<td>Imatinib for local and distant recurrence</td>
<td>Favorable response to therapy with a 35% reduction in the sum of measured lesions on CT at 3 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imatinib for distant recurrence unresponsive to CT</td>
<td>42% reduction in the summed size of target lesions on CT early. Then treatment stopped at 4 m due to disease progression. Patient died shortly after.</td>
</tr>
<tr>
<td>Janco et al., (26)</td>
<td>8</td>
<td>INF</td>
<td>Complete recovery, NED (n=2) Recurrence (n=2), after 22.8 &amp; 24 m Median RFS* = 18 m Median OS* = 21.6 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GM-CSF</td>
<td>Recurrence (n=3), after 7, 10.8, 20.4 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GM-CSF + RT</td>
<td>Recurrence after 3.6 m</td>
</tr>
<tr>
<td>Campaner et al., (6)</td>
<td>1</td>
<td>INF-α</td>
<td>Survived 7 m with NED</td>
</tr>
<tr>
<td>Tasaka et al., (27)</td>
<td>4</td>
<td>INF-β</td>
<td>Recurred within 12 m, mean RFS = 5 m, mean OS = 12.6 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INF-β + CT (dacarbazine, nimustine &amp; vincristine)</td>
<td>Recurred within 12 m, mean RFS 32.6 m, mean OS 46.3 m</td>
</tr>
<tr>
<td>Nai et al., (28)</td>
<td>1</td>
<td>Ipilimumab</td>
<td>Discontinued after 3 cycles due to failure of improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivolumab</td>
<td>Discontinued after 4 cycles due to hepatic insufficiency</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT: Chemotherapy; IL-2: Interleukin-2; INF: Interferon; NED: No Evidence of Disease; m: Months; RFS: Recurrence Free Survival; OS: Overall Survival; GM-CSF: Granulocyte Macrophage Colony-Stimulating Factor; RT: Radio Therapy * For All patients in the trial who received adjuvant therapy (n=10) (8 immunotherapy + 2 chemotherapy)
The prognosis of vulvar melanoma is very poor with a 5-year survival ranging from 9-55% compared to 50-80% 5-year survival in other cutaneous melanomas [1,4]. The main prognostic factors include the AJCC stage, Breslow’s thickness, tumor location, tumor thickness, ulceration, clinical melanosis and lymph nodel status [2,4]. The AJCC stage is the strongest independent prognostic factor for vulvar MM as AJCC stage 0-II is associated with better 5-year survival than stage III disease (63.6% versus 0%) [15]. Breslow’s thickness can influence recurrence as Breslow depth ≤1.75 mm is associated with 0% recurrence versus 100% in lesions deeper than 1.75 mm [31]. The primary tumor location can affect the outcome as central primary lesion has a greater risk for local nodal extension and recurrence compared to lateral lesions [1].

CONCLUSION

Vulvar melanomas are a unique subclass of mucosal melanomas that is molecularly distinct from cutaneous melanomas with KIT mutations being the most common genetic alterations. A biopsy is crucial for definitive diagnosis whereas pelvic MRI and PET/CT are essential imaging modalities for assessing local and distant spread. Wide local excision is the mainstay of treatment. Although vulvar melanoma is very aggressive with poor prognosis, molecular and immunotherapy are a helpful adjunct in advanced and recurrent cases.

REFERENCES

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