Vulvar malignant melanoma: A case report and review of its management

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Abstract

Vulvar malignant melanoma (VMM) is uncommon and poses a significant management challenge. Here, we presented a case of VMM managed by surgery, chemoradiation, and planned for targeted therapy. A 70-year-old woman with underlying diabetes mellitus and hypertension presented with a black-colored exophytic growth around her left vulva for two months. Initial biopsy confirmed malignant melanoma with positive staining for S100, HMB 45, and Melan A. An imaging study showed that the disease was localized to the vulva. She underwent bilateral radical vulvectomy and bilateral inguinofemoral lymph node dissection followed by radiotherapy. She had a locoregional disease recurrence, which was subsequently managed by palliative perineal radiotherapy, chemotherapy, and planned for immunotherapy. Vulvar malignant melanoma is a rare and aggressive tumor, with a poor overall prognosis, and high recurrence rate. Adjuvant chemotherapy, radiotherapy, and immunotherapy may be beneficial for local recurrence and distant metastasis cases. Molecular Analysis has a potential role in targeted therapy to improve the survival and outcome of the patient.

Introduction

About 4% of female reproductive organs and 0.6 percent of all cancers in women are caused by vulva cancer.[1] It contributes to less than 1% of all melanomas and is located in areas of unexposed ultraviolet radiation.[1-4] Despite its rarity, it is the second most common type of malignancy of the vulva after squamous cell carcinoma (incidence of 10%).[1,5] Given such rarity, the standard treatment is less clearly defined and is mainly extrapolated from the management of cutaneous melanomas.[1,3] Herewith is a report on a case of malignant vulvar melanoma and a discussion of the management approach.

Case Report

A-70-year-old multiparous woman with diabetes mellitus and hypertension presented with a black colored swelling around her left vulvar labium majus and minor. The swelling grew rapidly within 2 months. It was associated with foul odor, vaginal discharge, and per vaginal spotting. There were no constitutional symptoms, and no altered bowel or bladder habits. She had surgical menopause from a previous total abdominal hysterectomy and bilateral salphingo-oopherectomy (TAHBSO) for uterine leiomyoma 18 years ago. There was no family history of malignancy. On examination, her body mass index (BMI) was 39 kg/m^2. Breast and abdominal examinations were normal, with no significant palpable lymph nodes. An examination of the perineum revealed a pigmented left vulva measuring 6×4 cm with an irregular center and exophytic growth measuring 3×2 cm. The vaginal wall and vault were smooth without any pigmented areas, except for a 1 cm lesion located at the lower posterior vaginal wall area.

Histopathological examination of the biopsy taken from the left vulva lesion showed vulva tissue infiltrated by malignant cells arranged in solid sheets and clusters within the papillary dermis and dermis (Figure 1A). The tumor was composed of epithelioid to spindled cells associated with scattered intracytoplasmic melanin pigments. The epithelioid cells showed abundant eosinophilic cytoplasm and large nuclei with prominent nucleoli, while the spindled cells showed oval to elongated nuclei with moderate cytoplasm. Mitoses were up to 29/10 hpf. Focal nests of melanoma cells were also seen within the junctional zone within the dermis. No overt lymphovascular or perineural invasion was seen. The deepest tumor penetration was 4 mm. Immunohistologichemical (IHC) staining demonstrated tumor cells that were positive for S100, HMB45, and Melan A (Figure 1B,C,D) while negative for the keratin marker Pancytokeratin (Figure 1E), confirming the diagnosis of malignant melanoma of the vulva.

Contrast-enhanced computed tomography (CECT) of the thorax, abdomen, and pelvis showed a 4.8×4.7 cm hypodense mass in the perineum, extended and blended with the vulva anteriorly. Findings did not suggest any involvement of the supra levator area or adjacent organs. Similarly, there

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was no significant para-aortic, pelvic, or inguinal lymph node involvement. Following a multidisciplinary meeting (MDT) and detailed counselling on treatment plans, she opted for primary surgery with preoperative stage 2 disease.

She underwent bilateral radical vulvectomy and bilateral inguinal lymph nodes dissection (Figure 2). Intraoperatively, there were multiple small dark pigmented spots in the lower part of the posterior wall of the vagina with a normal urethral meatus and clitoris. The left superficial and deep inguinal were suspiciously enlarged. She had an uneventful postoperative recovery and good wound healing. She was discharged well 15 days after surgery.

Histopathological examination of the radical vulvectomy specimen revealed a malignant nodular tumor filling and expanding the skin papillary and reticular dermis (Clark Level IV) with overlying epidermal ulceration (Figure 3A). Tumor-infiltrating lymphocytes were brisk, with no overt lymphovascular or perineural invasion identified. Breslow's thickness was 5 mm. The tumor was located 2.5 mm from the nearest inner resection margin, 12 mm from the nearest outer resection margin, and 10.5 mm from the deep resection margin. The right vulva, vaginal wall, and lymph nodes were not involved by the tumor.

Subsequently, she received radiotherapy to the perineum for 50 Gray (Gy) for 20 fractions over 4 weeks given the inadequate surgical margins. Unfortunately, after 10 months, she developed acute urinary retention and recurrent growth at the urethral meatus, confirmed by biopsy. She required a suprapubic catheter insertion for bladder outlet obstruction. Repeated CECT of the thorax, abdomen, and pelvis showed a new mass in the vagina and right inguinal lymphadenopathy with no distant metastases.

She received perineal radiotherapy at 20 Gy for 5 fractions and completed 6 cycles of IV Dacarbazine 375 mg/m^2. Molecular mutational analysis was negative for BRAF. Following approval and availability from the National Cancer Council Malaysia, she was scheduled for IV Nivolumab (monoclonal antibodies checkpoint inhibitors) 200 mg 2-3 weekly for 6 cycles.

Discussion

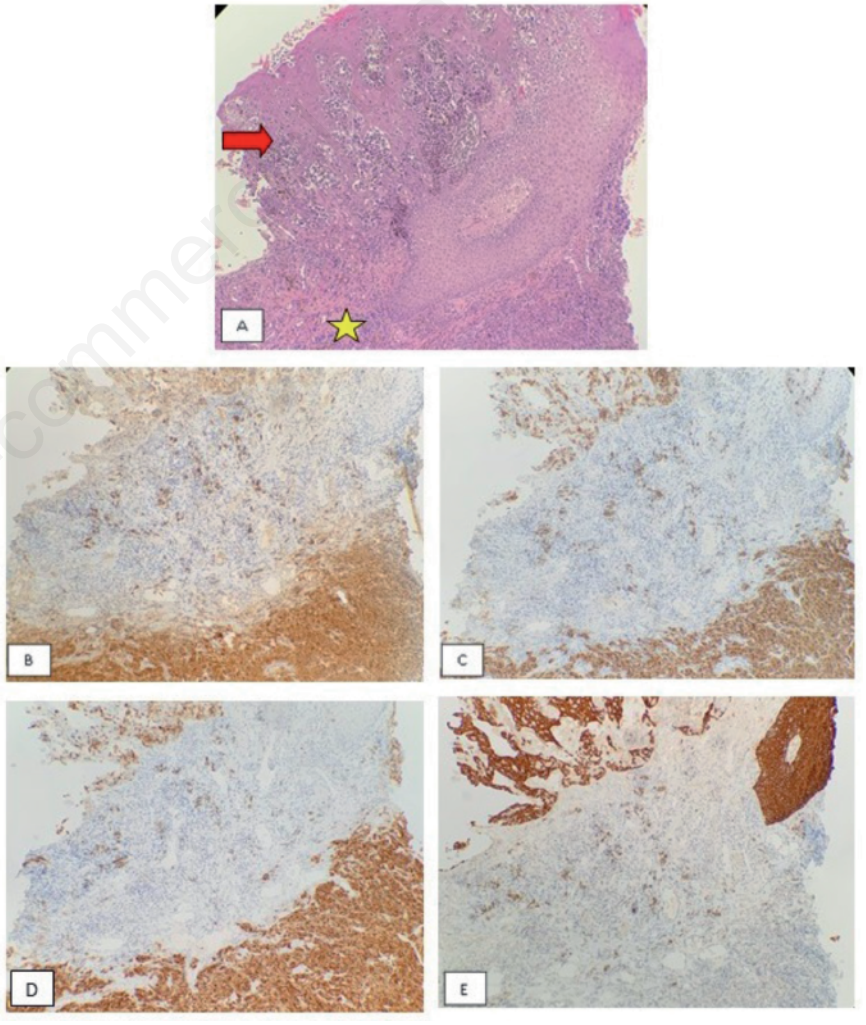
Malignant melanomas arise from melanocytes, with the skin being the most frequent site, about 90-91%.[2] Nevertheless, a small proportion of melanoma can develop in mucous membranes such as the nasal cavity, anorectum, and vulva-vagina area.[2] Vulvar malignant melanoma (VMM) represents 1 in 17 compared to cutaneous melanoma with a high recurrence rate.[1,4]

The pathogenesis of VMM is poorly understood but is found to arise *de novo* on the vulva since this area is not directly exposed to UV light.[3]

It occurs mainly in postmenopausal women in the fifth to seventh decade and is commonly seen in Caucasians.[2,3] The most common presenting symptoms are pain, bleeding, pruritus and vulva mass.[2,3] Patient may present late or during advanced disease due to the absence of early signs, low body awareness to this location, and being misdiagnosed with benign disease.[3,5] Approximately one-third of patients may present with lymph node involvement.[5]

The predisposing factors for VMM includes ulcerated lesion, previous local radiation, human papillomavirus infection, diabetes mellitus, or immunocompromised. In the case of our patient, her likely risk factors were advanced age, postmenopausal status, and diabetes status. It can cause metastasis to regional lymph nodes, lungs, bones, peritoneum, liver, and brain, with the lung being the most common site, followed by the liver and brain.[2,5]

Local tumor extension and soft tissue assessment are ideally done by pelvic MRI. Once vulva melanoma has been diagnosed, a total-body, skin, and eye examination is required to rule out other primary disease sites.[2] In view of the high propensity of local and distant spread, chest, abdomen, and brain multidetector computed tomography (MDCT) or whole-body PET/CT are used for remote staging if accessible. Although we had limitations with our local imaging modality, the available CECT information was sufficient for us to decide on a further management plan for her. Serum lactate dehydrogenase (LDH) may have value in the assessment of therapeutic



Vulva tissue infiltrated by melanoma cells within the papillary dermis (red arrow) and dermis (yellow star). A: H&E (x20) B: S100 (x20) C: HMB45 (x20) D: Melan A (x20) E: Pancytokeratin (x20).

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response.[2] Diagnosis of VMM is mainly based on tissue biopsy.[2] Epithelioid type is the most common histological cell types, followed by spindle and mixed type.[5] Immunohistochemical staining showed positive for S-100, HMB-45, and Melan-A, which are all evidence in this case. The S-100 presents the highest sensitivity (97-100%), while the Melan-A protein demonstrates the highest specificity (95-100%).[3]

VMM may have its own mutational signature that differentiates it from other subtypes of melanomas. KIT mutations are the most common mutations (15.3-35%) while NRAS (0-27.6%), BRAF (0-9%), and p53 (0-7.6%) mutations are less common or absent.[2,3] Vulvar melanomas frequently express programmed cell death 1(PD-1) (77%) and its ligand PD-L1 (54%).[2] BRAF mutation is associated with a more aggressive tumour.[5]

Currently, there are no standards or consensus guidelines in regard to the ideal management of VMM. Surgery is still the mainstay treatment of choice, especially in early stage disease.[4,6-8] Wide local excision with a 1 cm surgical margin is recommended for a lesion with a depth of less than 1 mm, and *en bloc* resection for deeper lesions with a safety margin of 2-3 cm and regional lymphadenectomy.[5] Nowadays, wide local excision is preferred over radical surgery in view of the poor prognosis of the disease, and both procedures have similar survival outcomes.[2,7-9] Even though radical surgery is associated with postoperative morbidity (lymphoedema and secondary disabilities) and does not influence the patient's survival, some gynae-oncologist still consider radical surgery as the only treatment approach for vulva melanomas given the lack of adjuvant therapy.[2] The challenge in obtaining a clear surgical margin is attributed to the anatomical position of this tumor near to the clitoris, urethra, or anus and the majority of patients presented in locally advanced stage (tumor thickness >4 mm).[3,7,8] Lymph node status is the most crucial prognostic factor, and positive nodes are a distant recurrent predictor.[3,7,8,10] Thus, elective bilateral inguinal lymphadenectomy is a standard procedure, even though this has no impact on overall survival.[3,7,8,11]

There are various staging systems used for VMM, including Clark's original system 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 classification based on level of histological involvement; FIGO staging based on tumor size, lymph node status, distant metastases and AJCC 8th edition based on tumor thickness, ulceration, nodal status, distant metastasis and serum lactate dehydrogenase (LDH) level.[2] In VMM, staging based on the Breslow, Clark and Chung systems is more commonly used because they have better correlation and prognostication.[1,7,8,12]

A combination of chemotherapy involving cisplatin, vinblastine, dacarbazine, temozolomide, tamoxifen, IL-2, and IFN-A has a median survival of 10 months, with 36% having a partial response for advanced VMM. Radiotherapy in VMM has improved local control, but it showed no benefit in overall survival.[3] Fourteen months of progression-free survival is linked to Nivolumab, a monoclonal antibody called PD-1.[2,10]

Some literature demonstrates that 5-year survival rates are around 20-56% irrespective of disease stage.[5] Poor prognostic features and poor radiotherapy responses are; ulceration, Breslow and Clark level V, positive surgical margin and lymph node involvement. In addition, patients with these features tend to develop recurrent, both local and distant.[5]

Conclusions

Vulvar malignant melanoma is an extremely rare and aggressive tumor with a poor overall prognosis and a high recurrence rate. Primary surgical treatment is based on the balance between several factors, including maximizing progression-free

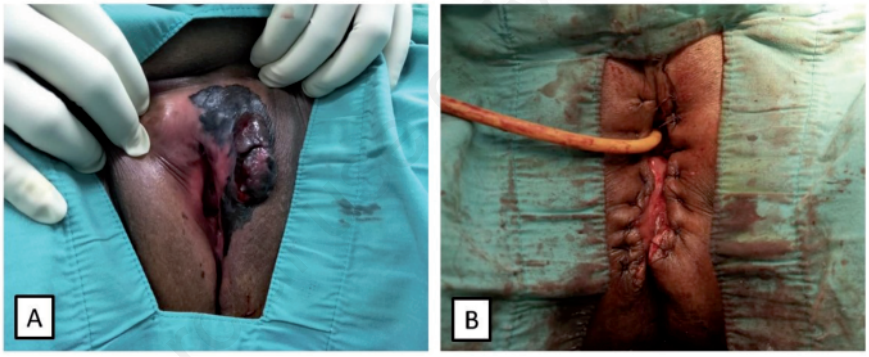

Figure 2. A) The lesion prior to surgery and B) post radical vulvectomy.

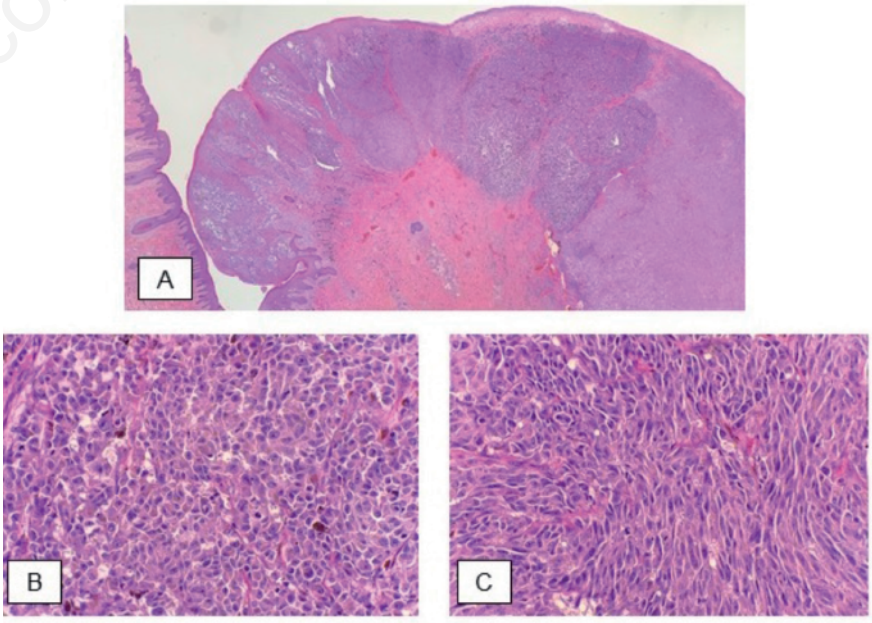

Figure 3. Nodular tumor with tumor cells filling and expanding the skin papillary and reticular dermis. A: H&E (x20) B: Epithelioid tumour cells, H&E (x40) C: Spindled tumour cells, H&E (x40).

survival, local disease control, minimizing operative morbidity, bodily function, and quality of life. Adjuvant chemotherapy, radiotherapy, and immunotherapy may be beneficial for local recurrence and distant metastasis cases. Molecular Analysis has an identifiable role in VMM management. When tailored with targeted therapy or immunotherapy, it may improve progression-free survival and the outcome of the patient.

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