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Multimodality treatment of a primary vulvar melanoma in a low resource setting: A case report

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ABSTRACT

Primary vulvar melanoma is a rare but highly aggressive malignant neoplasm accounting for 1–2 % of all malignant melanoma and 5–10 % of all vulvar cancers in females. Here we report a case of 32 years old female diagnosed with primary vulvar melanoma during the evaluation of a two cm growth in the inner labia minora on the right side. She underwent wide local excision with excision of the distal one cm of the urethra and bilateral groin node dissection. The final histopathology was vulvar malignant melanoma with 1 out of 15 groin nodes involved but all resected margins were free of tumor. The final surgical stage was T4bN1aM0 (8th AJCC TNM) and IIIC (FIGO). She received adjuvant radiotherapy followed by 17 cycles of Pembrolizumab. To date, she is both clinically and radiologically disease free with a progression-free survival of 9 months.

1. Introduction

Malignant melanoma (MM) is a highly aggressive tumor of the skin, eyes, and mucous membranes accounting for less than 1 % of all cancers (Morrow and DiSaia, 1976). This tumor is derived from the basal layer of melanocytes formed during embryogenesis from the neural crest of the trunk (Mort et al., 2015). In recent years, the incidence of primary gynecologic melanomas (GM) is increasing and is estimated to be 1.74 per million females. GM are rare neoplasms accounting for 3–7 % of all MM in the female with the majority occurring in the vulva and vagina and rarely in the ovary, uterus, and uterine cervix (Vyas et al., 2016). Primary vulvar melanoma (VM) accounts for 1–2 % of all MM in females which only occupy 1 % of the total body skin area suggesting an increased predisposition of the vulva for the development of melanoma (Heinzelmann-Schwarz et al., 2014; ul Ain and Rao, 2020).

The aim was to discuss the clinical presentation, diagnostic dilemma, literature review, and multimodality treatment of vulvar melanoma in a low-resource setting in Eastern Nepal.

2. Case report

A 32 years old unmarried female presented in the gynecological outpatient department with a growth in the perineal region for two weeks. She had a normal body mass index and no significant medical, surgical, family, or menstrual history. Her physical and systemic examination was normal. On local examination, there was 2 cm vascular and black pigmented growth arising from the labia minora and distal vagina, the rest was normal (Fig. 1). Her cystoscopy was normal. Excisional biopsy showed atypical cells containing intracytoplasmic melanin pigments which were positive for SOX10, MELAN A, and HMB45 on immunohistochemistry (IHC) confirming malignant melanoma (Fig. 2a–e). MRI of the pelvis showed a 3.5 cm mass arising from the right labia minora/distal vaginal wall with involvement of paravaginal tissue, rest normal. CT upper abdomen and chest were normal (Fig. 3). There were no other melanotic foci seen on colonoscopy, ophthalmoscopy, and detailed dermatological examination. Subsequently, the patient underwent wide local excision of the growth with excision of the distal 1 cm of urethra obtaining at least 1 cm tumor-free surgical margin and bilateral saphenous vein sparing groin node dissection. The duration

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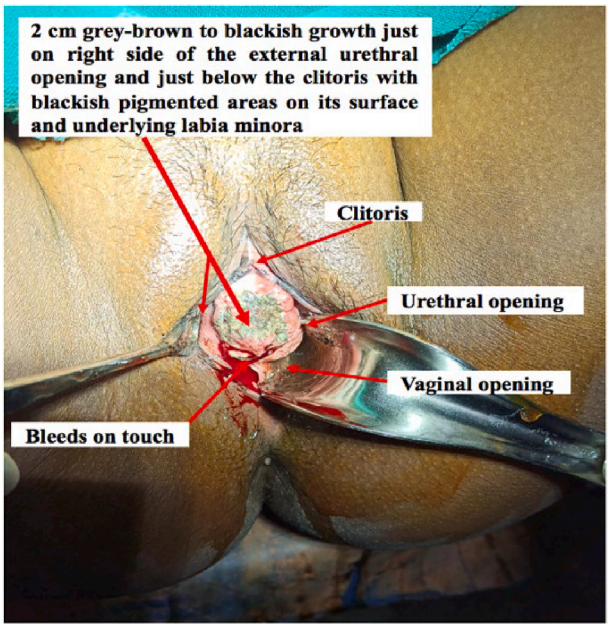

Fig. 1. Growth as described arising from the right labia minora and distal vagina which bleeds on touch.

of surgery was 4 hours with a blood loss of 250 ml. Bilateral groin drains were removed on the 23rd postoperative day. Her duration of hospital stay was 26 days with postoperative Clavein Dindo complication grade II (complication type - perineal wound infection/breakdown on 6th postoperative day managed by daily wound care) and the duration of Foley catheterization was 6 weeks (Fig. 4a–f). The final histopathology was Malignant Melanoma, Not Otherwise Specified (NOS) with a tumor site in the vulva and urethra involved. Grossly, the melanotic growth measured 2.7 × 1.7 × 1 cm. The growth was 1.2 cm from the superior, 1.3 cm from the inferior, 2.5 cm from the left lateral, and 0.9 cm from the right lateral margin but only 0.2 cm from the base. A total of 15 groin nodes (LN) were retrieved: 7 from the right (4 superficial, 3 deep) and 8 from the left (all superficial). Breslow's tumor thickness was 1.1 cm and Clark level V due to invasion up to the subcutis (spread down into the tissue beneath the skin). All the peripheral (superior, inferior, right lateral, and left lateral) and deep margins were uninvolved by the tumor. Mitotic figures were 8/10 hpf, ulceration present but lymphovascular space invasion was absent. One of the left superficial groin nodes was involved. Hence, the final stage was T4bN1aM0 as per the 8th AJCC TNM staging system (FIGO stage IIIC).

As per the tumor board decision, she received external beam radiation therapy (Intensity Modulated Radiation Therapy) of 60 Gy in 30# (2 Gy/#) at the primary site and bilateral groins at an external cancer hospital 300 km away in the capital city followed by 17 cycles of intravenous Pembrolizumab 100 mg × 3 weekly at the parent institute. Her family managed the surgical and radiotherapy treatment using the government cancer scheme fund of 760 USD (Nepalese Rupees 100,000). For immunotherapy, Pembrolizumab was obtained directly from an international pharmaceutical company costing 1396 USD (Nepalese Rupees 184,267) per cycle. The cost of this immunotherapy, its response rate, and survival benefits based on few studies of the use of immunotherapy in metastatic (e.g. nodal involvement) vulvar melanomas and extrapolated data of their uses in cutaneous melanomas were carefully discussed between the family members, patient and the tumor board teams (medical and surgical teams) and they opted for it despite the cost. Her family managed these expenses by selling one-half of their apartment, making a significant sacrifice for her treatment. Immediately following radiotherapy, the patient developed radiation-induced vaginal fibrosis and stenosis presenting frequently with retention of urine requiring indwelling catheterization so she underwent a vaginoplasty to make the external urethral opening free and ease her voiding function (Fig. 4g, h). During the later few cycles of immunotherapy, she developed hypopigmented areas on her forehead and forearms managed with systemic steroids. Following treatment completion, radiological imaging of the whole abdomen and chest showed no evidence of disease. After treatment completion, she developed left leg lymphedema with lymphangitis managed with oral antibiotics and short-course oral steroids after the Doppler study was normal. To date, she is disease free both clinically and radiologically with a progression-free survival of 9 months.

3. Discussion

Malignant melanomas (MM) are categorized into cutaneous and noncutaneous melanoma (noncutaneous further divided into ocular and mucosal melanoma). Gynaecologic melanoma (GM) which falls in the mucosal subtype has lower five-year survival than that of cutaneous melanoma (25 % vs 81 %, respectively). The delay in diagnosis as a result of tumor location and rich lymphatic and vascular network of the female genital-tract mucosa might be the contributing factors for early tumor spread and development of metastases resulting in lower survival and poor prognosis (Dunton and Berd, 1999). VM accounting for 76 % of female genital tract melanoma is the most common among all GM. VM accounts for 5–10 % of all vulvar cancers and ranked second as the most

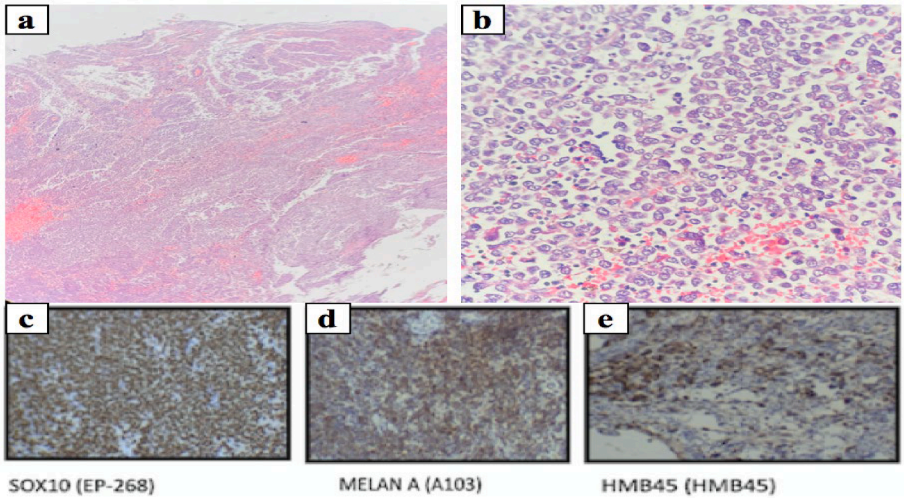

Fig. 2. a-Proliferation of atypical cells predominantly in sheets, lobules and nests transversed by fibrovascular cores with focal connection to the basal layer of overlying squamous spithelium, ulceration present (H&E staining, 40× Magnification). b-Atypical cells show moderate to marked plemorphism, round to oval to spindle shaped nuclei, high N/C ration, irregular nuclear membrane, hyperchromatic to vesicular chromatin, predominant nucleoli, eosinophilic to clear cytoplasm and contain intracytoplasmic melanin pigments as well. Frequent atypical mitotic figures (6/10vHPF) along with of geographic necrosis and bizarre Multinucleated tumor cells having sarcomatoid morphology observed (H&E staining, 400xMagnification).c, d,e-The tumor cells were positive for SOX10, MELAN A and HMB45.

common vulvar cancer after squamous cell carcinoma with an incidence of 0.2 per 100,000 females a year (Stang et al., 2005; Sugiyama et al., 2007). VM usually presents in the fifth to seventh decades of life and is more common in white ethnicity. However, Wohlmuth et al. (Wohlmuth et al., 2020) reported its occurrence at a significantly younger age ($p < 0.001$) Which is consistent with our patient presenting at an age of 32 years. Its presenting features are similar to those of other vulvar cancers like pruritus, bleeding, ulceration, vulvar growth, pain, discharge, micturition discomfort, irritation, etc (Sugiyama et al., 2007). They usually originate from the labia minora (around 38 %), the clitoris (around 12 %), or the inner non-hairy part of the labia majora (around 51 %). In our patient, the site of origin was in the non-hair-bearing area near the labia minora. Whole-body skin examination and ophthalmological assessment are mandatory to rule out other melanotic foci that have metastasized to the gynecological organs. Because of the propensity to distant spread, thorough radiological work-up (including brain imaging and PET-CT if available) and analysis of serum lactate dehydrogenase are needed to exclude metastatic disease (Takehara et al., 2002). However, in our patient, an MRI pelvis, CT upper abdomen and chest, colonoscopy, ophthalmoscopy, and dermatological examination were reviewed which showed no regional or distant metastasis or presence of melanotic foci elsewhere in the body. Though PET-CT is ideal for metastatic workup in such an aggressive disease, it was not done in our patient due to the unavailability of the service locally. The recommended surgery in the past was radical vulvectomy, irrespective of tumor thickness, level of invasion, size, and site. However, conservative surgery in the form of wide local excision has widely been accepted nowadays over radical vulvectomy (Suwandinata et al., 2007). Irving et al. found no difference in survival for patients undergoing radical vulvectomy or simple vulvectomy or wide local excision. Regarding the extent of vulvar resection, there is no significant difference in survival noted comparing the tumor-free lateral surgical margins of less than 2 cm to more than 2 cm. Sentinel lymph node (SLN) biopsy is reliable to address the regional lymphatic basin without dissecting the entire drainage basin (Irvin et al., 2001). The detection rate of SLN biopsy was almost 100 % with a negative predictive value of more than 85.0 % (Dhar et al., 2007). IHC has its important clinical utility in the differentiation of melanoma from other vulvar soft tissue lesions of epithelial, mesenchymal, or neural origin. Melanomas are usually immunoreactive for Melanoma antigens like melan A, S-100 protein, melanoma-specific antigen (HMB-45), SOX10, etc. S-100 protein has a high sensitivity of 97–100 %, while HMB45 and Melan A have high specificity of 95–100 % (Orchard, 2000). Currently, there are no perfect staging systems and treatment guidelines for GM including VM. The International Federation of Gynecology and Obstetrics (FIGO) staging system being used for vulvar squamous-cell carcinoma is considered a weak predictor of survival and treatment decision compared to micro staging systems like Clark's level, Breslow's thickness and Chung's modified Clark system (Ragnarsson-Olding et al., 1999). The American Joint Committee on Cancer (AJCC) melanoma staging system is the most significant predictor of survival in vulvar melanoma so the revised 8th AJCC 2002 melanoma staging system has been proposed for vulvar melanoma (Kim et al., 2002). Before the era of precision therapy, the treatment of VM includes surgery, chemotherapy, and/or radiotherapy. Preoperative neoadjuvant radiotherapy is useful to shrink tumor size and achieve more conservative surgery or as adjuvant therapy for positive margins or lymph nodes or as palliative therapy for metastatic disease (Piura, 2008). In our patient, the decision for postoperative adjuvant radiotherapy was made due to regional (groin) lymph node involvement despite negative margins (8th AJCC TNM staging-T4bN1aM0). Although adjuvant radiotherapy might reduce the risk of local or pelvic recurrence, it did not translate to improvement in overall survival between patients who did and did not receive adjuvant radiotherapy because the risk of distant recurrence was not reduced (Frumovitz et al., 2010). Chemotherapy is mainly used in neoadjuvant settings or in locally advanced or distant metastatic forms, utilizing the same agents as in cutaneous melanoma like cisplatin-paclitaxel, dacarbazine, and temozolomide (Gadducci et al., 2018). In VM, the most frequently expressed molecular markers are topoisomerase IIa (TOP2A) (89 %), PD-1 (75 %), PD-L1 (56 %), and phosphatase and tensin homolog (PTEN) (56 %). Among the gene analyzed using gene sequencing, BRAF was the most frequently mutated (26 %) followed by KIT (22 %) and adenomatosis polyposis coli (APC) (10 %) (Hou et al., 2017). High expression levels of PD-1 and PD-L1 in patients with VM highlight the

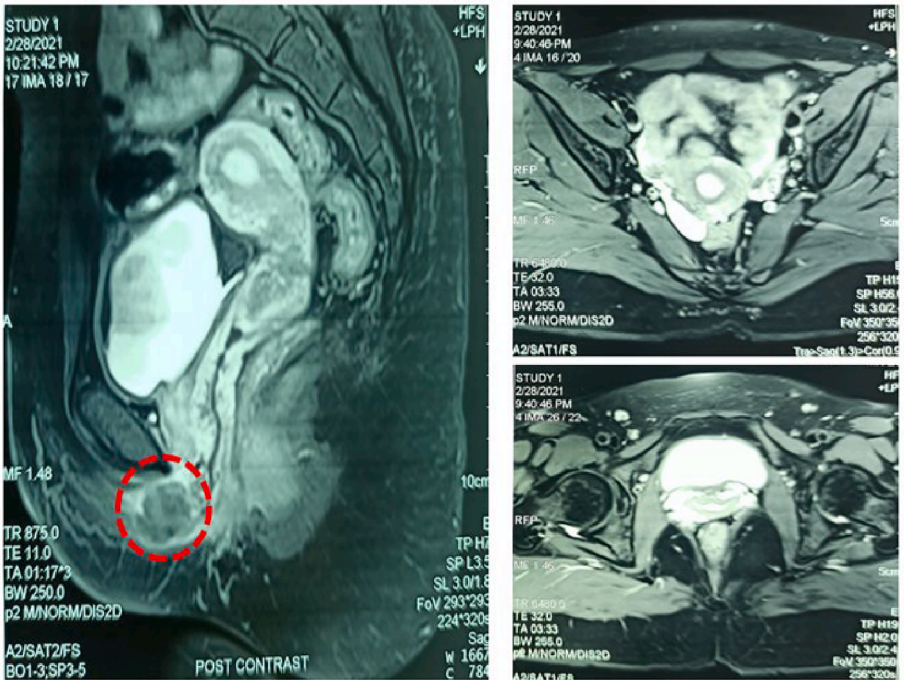

Fig. 3. MRI pelvis showing 3.5 × 2.9 cm lobulated mass arising from the distal vaginal wall predominantly in the right side and extending to the introitus with involvement of paravaginal tissue but no urethral, pelvic or inguinal lymph nodes involvement.

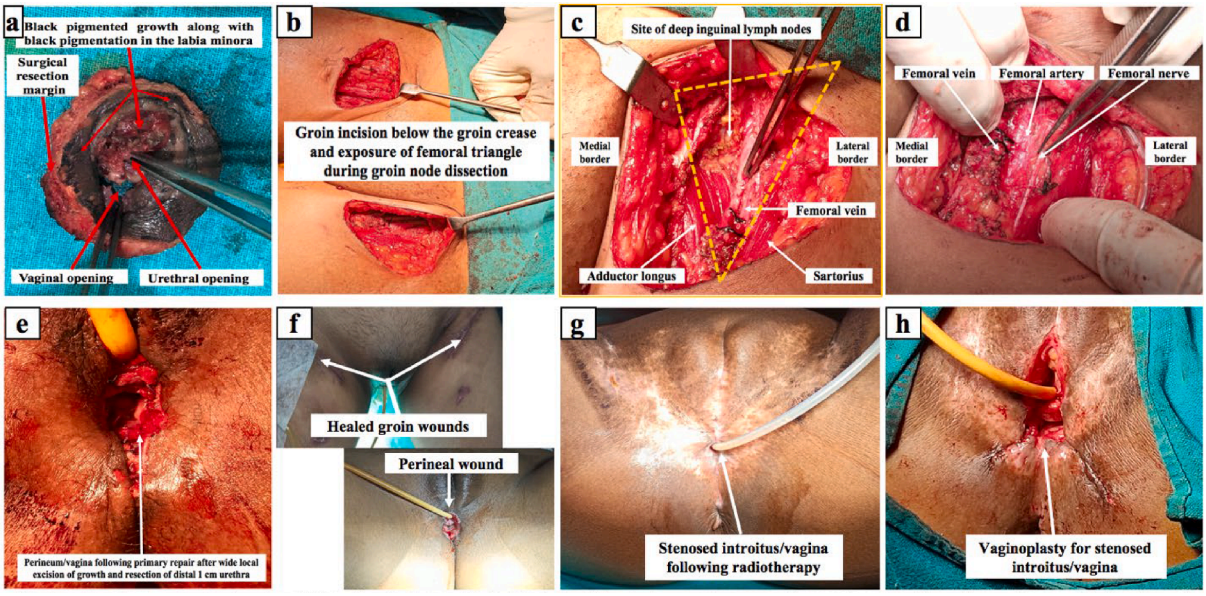

Fig. 4. a-Specimen of wide local excision of vulval growth. b-Groin incision below groin crease for groin node dissection. c-Femoral triangle and boundary. d-Contents of fermoral triangle (Vein antery, nerve from M → L). e-Perineal wound following primary repair. f-Healed perineal and groins wound at 6 weeks. g-Stenosed vaginal introitus after radiotherapy requiring indwelling catheter. h-Vaginoplasty to release stenosed vaginal introitus with bilateral episiotomy.

potential therapeutic option in the form of immunotherapy (e.g. Ipilimumab, CTLA-4 inhibitor; Nivolumab and Pembrolizumab, PD-1 inhibitor) for these patients (Hou et al., 2017). Since PD-1 or PD-L1 are highly expressed in vulvar melanoma, IHC for these immunomarkers was not done in our patient due to the unavailability of the service locally and the need for repeat outsourcing of blocks or specimen to neighboring country (India), additional cost (69 USD) and time lag (3–4 weeks). PD-1, CTLA-4, and PD-L1 are targets for immunotherapy in many malignancies so treatment with Pembrolizumab was started in our patient based on the fact that these immunomarkers are highly expressed in vulvar melanoma. However, some genital melanomas have benefited from immunotherapy regardless of the immunochemical PD-1 or PD-L1 status (Yu et al., 2020). Besides, PD-L1 expression may simply have a prognostic role as low PD-L1 expression had shown better overall survival in one series (Chłopik et al., 2018) while unaffected in another series (Yu et al., 2020). Similarly, BRAF gene mutation was not checked in our patient due to the unavailability of gene sequencing locally. BRAF mutation is often represented by the V600E, a target of Trametinib and Dabrafenib. In addition, Hou et al. showed that 63 % of vulvar melanomas with BRAF mutation express TUBB3, a marker of resistance to taxanes (Hou et al., 2017). Women with metastatic VM treated with immunotherapy (PD-1 inhibitors or a combination of CTLA-4 and PD-1 inhibitors) had an objective response rate (ORR) of 37.5 % (95 % CI = 13.8 %–61.2 %, p = 0.184) and clinical benefit rate (CBR) of 62.5 % (95 % CI = 38.8 %–86.2 %, p = 0.023) with median progression-free survival of 9.0 months (95 % CI = 1.9–16.1 months, p = 0.062) (Wohlmuth et al., 2021). The response rate is lower compared with cutaneous melanomas (60.0 %) but the safety profile and immune-related adverse events were comparable (Wohlmuth et al., 2021). Hence, adjuvant treatment with immunotherapy should be discussed in patients with metastatic (e.g. nodal involvement) or unresectable melanoma. In our patient, Pembrolizumab was added in the adjuvant setting considering the regional lymph node involvement (groin node), young age, and its behavior. The tumor board team (medical and surgical teams) had a careful discussion with the patient's family about the cost, response rate, and survival benefits of adding Pembrolizumab in the adjuvant setting in melanoma with nodal involvement and the family opted for the treatment despite the cost. However, we lack any local or national level ethical board for discussion of these difficult decisions. Vulvar melanoma is usually highly aggressive with a tendency to recur locally and develop distant metastases. The 5-year survival (mean 36 %) is lower compared with cutaneous melanoma (mean 81 %), ocular melanoma (mean 74 %), and vulvar squamous-cell carcinoma (mean 72 %) (Irvin et al., 2001; Orchard, 2000). Age at diagnosis, tumor size, lymph node involvement, number of involved nodes, mitotic count, tumor thickness, AJCC's stage at diagnosis, etc. are the strong independent predictors of survival. Local recurrence is closely related to tumor size, while distant recurrence is related to the lymph node involvement and AJCC stage of disease (Iacoponi et al., 2016; Raspagliesi et al., 2000).

4. Conclusion

Although VM is a rare mucosal melanoma, attention should be given to any suspicious pigmented lesions on routine examinations, and the threshold to biopsy suspicious lesions should be kept low. Knowledge of this disease is poor and, so is knowledge of the prognosis. Early diagnosis and application of the appropriate multimodality therapy centered on the surgery could improve the prognosis of this disease. VM constitutes a high-risk group with delayed diagnosis and dismal prognosis. Hope has grown out in recent years with immunotherapy and should be offered to women with metastatic or unresectable VMs.

5. Patient's view about her cancer

"Dear cancer…! You are going to be only a short chapter not a story in my life. Since the day you came into my life, both I and my family have been struggling a lot physically, socially, and financially to get through you. But I know I definitely will be winning. You may have started your journey with excitement but I will overcome you with the full power of my positivities. You may go now…!
Let's unite together to fight against all sorts of cancer."

Author contributions

R. S. wrote the manuscript in consultation with K. D., B. D. T., M. D., S. S., S. D., M. C. R., and B. H. O. S. D. helped in the conceptualization of the project. M. C. R., S. D., and B. H. O reviewed the manuscript draft and revised it critically on intellectual content. All authors supervised and approved the final version of the manuscript to be published.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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