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**VULVAR MELANOMA. A CASE REPORT AND REVIEW OF LITERATURE.**

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**ABSTRACT**

Vulvar cancer accounts for approximately 2- 5% of all gynaecological malignancy. The histologic subtype of melanoma is a rare entity. Steady increase in life expectancy of women has made these cancers more important as these malignancies are more common in 6<sup>th</sup> to 7<sup>th</sup> decade of life and later. Here the authors are presenting a case of vulvar melanoma diagnosed at stage-II managed by radical vulvectomy with inguinofemoral lymphadenectomy followed by postoperative radiotherapy. Review of literature regarding etiopathogenesis, management and followup of vulvar melanoma are also discussed.

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**INTRODUCTION**

Vulvar malignancies represent approximately 2-5% of all gynaecologic malignancies and 0.5% of all malignancies in female.[1,2] On histopathological subtypes vulvar melanoma is rare as comparison to squamous cell type and accounts for approximately 4-10% of all vulvar malignancies.[1,2] Vulvar melanoma accounts for 3 to 5% of all malignant melanomas in women even though vulva covers only 1% to 2% of the body surface.[2] Predominantly these lesions are more common in white women than heavily pigmented races in their 5<sup>th</sup> to 8<sup>th</sup> decade.[1,2,3] The estimated incidence available in literature is 0.1 to 0.19/100000 population.[4] The most common presenting symptoms are bleeding from the genital, a lump

or a changing mole and pruritus or irritation. The most common site of origin of vulvar melanoma is from labia minora, labia majora or clitoris. [1] As this is an uncommon disease the literature on this topic is only case reports or series of small number of patients and hence the behaviour of this tumor is difficult to define and the treatment modalities are still evolving. In general the behaviour of vulvar melanoma are similar to that of cutaneous melanomas and may be best predicted by a microstaging system and the course of regional metastasis is same as that of squamous cell cancer type. Hence the treatment of vulvar melanoma is individualized bases on clinic-pathological factors, microstaging and general treatment of cutaneous melanomas.[2,5]Pigmented vulvar neoplasia may be VIN, squamous carcinoma or pagets disease other than melanoma. So, tissue sampling is necessary and immunohistochemical studies and electron microscopy may help to confirm diagnosis.

Here the authors are reporting a case of primary vulvar melanoma in a black woman and the best available literature review.

### **CASE REPORT**

A 70 year old para10, postmenopausal for 30 years, presented to LNH gynecology out patient department with complaints of itching in vulvar region, discharge per vaginum and mass on the vulva for past two month. The growth was initially small in size which had increased progressively over two month duration to the presenting size and associated with bleeding and offensive discharge. For the past two months she had history of loss of appetite and weight. There was no significant past and family history. On general examination she was cachecxic with BMI of 16 Kg/m<sup>2</sup>.On per abdomen examination there was no significant finding. On local examination there was a greyish red growth of size 4×3cm arising from inner side of the right labia minora approximately one cm away from clitoris was irregular vegetative and ulcerated with bleeding from the center of the tumor on touch.(Fig-1)There was no extension of tumor into the vagina or urethra. On per speculum examination cervix and vagina was healthy but atrophic. On per vaginal examination uterus was small, anteverted and bilateral fornices were free and non tender. There were no palpable inguinal lymph node. A provisional clinical diagnosis of FIGO stage II(Tumor confined to Vulva and more than 2 cm in greatest dimension) vulval malignancy was made. A punch biopsy from the growth taken sent for histopathological examination which revealed abundant atypical cells dispersed in loose cluster with cells showing moderate nuclear atypia, opened up nuclear chromatin, inconspicuous nucleoli in modearate amount of cytoplasm and background of hemosiderin laden macrophages suggestive of malignancy. She was planned for modified radical vulvectomy and inguino

femoral lymphadenectomy and operated on August 2015. Intraoperative both side full chain of inguinal lymph nodes sent for frozen section which ruled out metastasis so pelvic lymphadenectomy was not done. The gross pathological examination of the specimen demonstrated 3×3×3 cm growth with soft tissue margin of 1.1cm anteroinferiorly and 0.6 cm posteroinferiorly.(Fig-2) Multiple sections examined from the growth showed a markedly cellular lesion composed predominantly of polygonal cells, focal spindling. The cells have moderate amount of eosinophilic cytoplasm, large vesicular nuclei and prominent macronucleolus with frequent mitotic figures seen. Few cells with intracytoplasmic brownish black pigment were seen. There was no evidence of perineural or vascular invasion seen. All sideways and deeper tissue margin of resected tissue were free of tumor margin. No tumor invasion seen in clitoral tissue and other side of labia. On immunohistological study the tumor cells expressed HMB-45 and S-100 and were negative for CK. (Fig-3)Overall diagnosis of malignant melanoma of vulva was made. Only one lymph node of ipsilateral side was found to have malignant deposit. Her postoperative care was given by antibiotics and local wound dressing. She was planned for postoperative external beam radiotherapy and completed in October 2015. She is now on follow up and doing well without any complaint or complication.

## DISCUSSION

Vulvar melanoma is the second most common histological type of vulvar cancer next to squamous cell cancer of the vulva. It has a very poor prognosis.[6] Unlikely to cutaneous melanomas which are associated with UV radiation the vulvar melanomas occur in sunshelded area and have the different etiology. These melanomas are more dense nearly the density of melanomas in chronically sun exposed skin of head and neck than melanomas on the other body surface. Most vulvar melanomas were located on the glabrous skin as opposed to the hairy skin within the vulva and differed significantly in biological properties. Diagnosis of vulvar melanoma is done by excisional biopsy and larger growths can be diagnosed by incisional biopsy. Treatment is by radical dissection of growth with 1 cm margin all around, clitoris, distal portion of vagina and with or without lower 1/3<sup>rd</sup> of urethra. Elective inguinal lymphadenectomy is advised for tumors of >4mm thickness. As with squamous cell carcinoma pelvic lymphadenectomy is not required for vulvar melanoma because the overall incidence of lymph node metastasis in vulvar melanoma is reported to be 30%. Pelvic lymphadenectomy does not appear to be warranted for a melanoma confined to the vulva with negative inguinal lymph nodes. The role of pelvic lymphadenectomy in patients with positive inguinal lymph

nodes is controversial and limited role because of poor prognosis. The role of elective radiotherapy to the regional lymph nodes in melanoma patients is unclear and should be used cautiously. After primary surgical therapy if high risk features identified like positive lymph node or deep invasion, effective adjuvant treatment has not yet identified. Radiotherapy may improve locoregional control of disease. Recurrent or metastatic disease carries a very poor prognosis in vulvar melanoma patients. Palliative systemic therapy consists of immunotherapy, chemotherapy(Dacarbazine), hormonal therapy(Tamoxifen) or all three. If during follow up isolated metastasis appear in an undissected groin, they should be excised.[2]

According to FIGO report 2015 majority of vulvar melanomas occur in clitoris and labia minora, and the recommended staging system to be Clarke/Breslow's modification of microstaging system which measures depth of invasion in histopathology, instead of the commonly used TNM/FIGO staging system.[7] Three histologic subtype of vulvar melanoma have been described: superficial spreading melanoma, nodular melanoma and acral lentiginous melanoma.[1] The prognostic indicators include the size of tumor and depth of invasion/thickness of tumor and ulceration as in cutaneous melanoma. The regional prognostic factors include the metastasis to lymph nodes(number), macroscopic vs. microscopic metastasis and the presence of clinical or microscopic satellite around a primary tumor. In advanced disease with distant metastasis, the site and number of metastasis and an elevated serum lactate dehydrogenase are most predictive of poor survival. Tumor of less than 7mm thickness has negligible chance of lymphnode metastasis but elective lymphadenectomy in these patients improves survival and prevent recurrences. [1]

For the treatment of vulvar melanoma recently there is trend towards more conservative resection of vulvar melanoma as it is followed for cutaneous melanoma.[8,9,10] Primary growth of the vulva should be treated by radical local excision of at least 1cm margin. The role of lymph node dissection is controversial. A multiinstitutional RCT on elective node dissection vs. observation for 1-4mm thickness melanomas in 740 patients reported significantly better survival with elective node dissection for young patients of less than 60 years age and with tumor 1-2mm thickness and patients without tumor ulceration. [11]

Study in 2000 reported incidence of occult inguinal lymph node is less than 5 percent for thin melanomas of <1mm and >70% for lesions of >4mm. [12] Recent trials suggest that adjuvant therapy with interferon-alpha may improve survival in patients with cutaneous melanomas but trials are not found in vulvar melanoma cases due to small number of patients and the tolerability of interferon is a barrier to patient acceptance. On multivariate analysis in one study

shows tumor thickness and ulceration along with macroscopic amelanosis, angioinvasion or DNA non-ploidy were usually the the significant predictors of poor prognosis. [13]

Quadrivalent HPV vaccines can prevent vulvar cancer caused by HPV types 6 and 11. Other preventable vaccines are under study. A large study compared the median survival of vulvar malignancy patients in black and nonblack population and showed the median survival for black patients was 16 months vs. 39 months in nonblack population and both are significantly low in vulvar group than cutaneous melanoma group. [14]A study included 85 patients of melanoma of female genitalia showed the survival rates at 1, 5 and 10 years were 85%, 51% and 30 % respectively. Higher survival rates were seen in those who received wide local excision. Despite the new treatments developed and attempted, there is no evidence that survival has improved over the past 40 years. Patients with thinner melanomas amenable to surgical resection had a better prognosis than those with more extensive, metastatic disease at presentation. [15] Sentinel lymph node biopsy is feasible but has limited role with 15% false negative rates in the management of vulvar melanoma.[16,17] A molecular diagnostic study of vulvar melanomas showed expression of p53 and c-KIT mutations and may enable therapeutic options in the future. Pathological classifiers, such as satellitosis, in-transit metastasis, LVSI and dermal mitosis can stratify patients who would profit from the investigation into c-KIT expression and the subsequent imatinib treatment. Imatinib is a targeted oral therapeutic agent against cutaneous melanomas.[18] A study showed efficacy with Imatinib treatment in vulvar melanoma.[19] Generally vulvar melanoma has poor prognosis and show a tendency to recur locally and develop distant metastasis through hematogenous dissemination. Death from vulvar melanoma is from the effects of widespread metastatic disease involving lungs, liver, and brain. The 5 year survival is 60 percent with decreased survival as age advances. Increasing age and African-American/black race is significant independent predictor for decreased survival. [20]

**CONCLUSION-** Patients with malignant vulvar melanoma require multidisciplinary approach involving gynaecologic oncologist and radiotherapy expert for management. Surgery is still the gold standard of treatment for curing malignant vulvar melanomas and should be performed in a gynecological cancer center. Less radical surgery presents a more realistic option for many patients without decreasing their survival rates. In high risk groups more studies into the genetic background are required to develop targeted treatment options.

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Figure 1: Local examination view during surgery showing growth on the right labia minora.



Figure 2: Gross specimen after radical vulvectomy showing growth on the right labia minora.

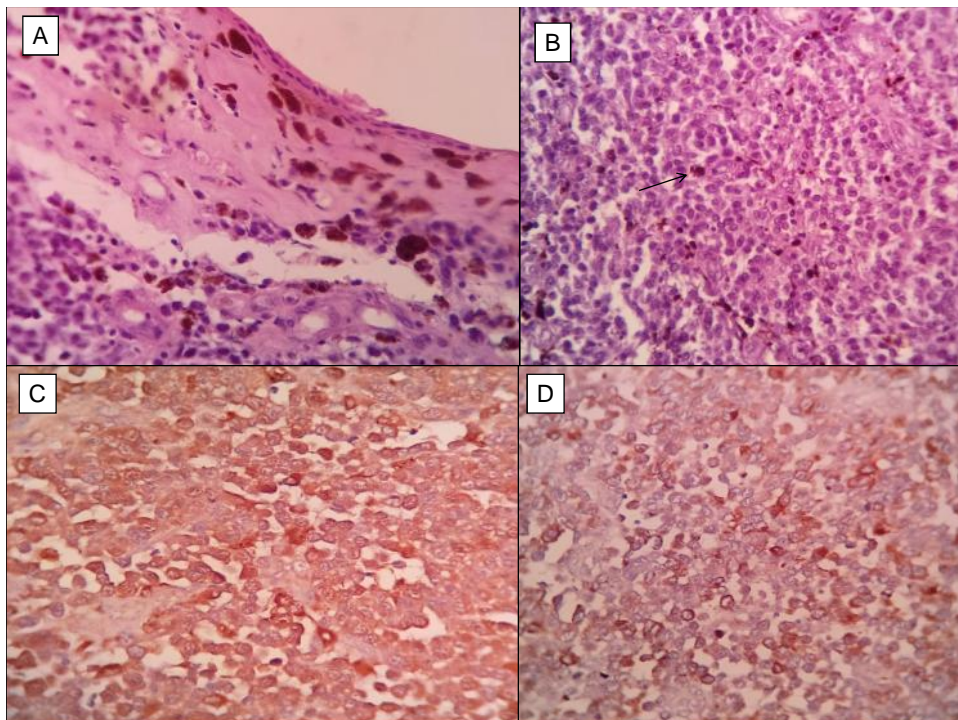


Figure 3: **A.** Photomicrograph showing tissue lined by unremarkable stratified squamous epithelium and presence of a markedly cellular tumor showing presence of cytoplasmic brownish black pigment. ( Hematoxylin and Eosin, 40 x)

Figure **B**. Photomicrograph showing sheets of large polygonal cells with a large opened up nucleus and prominent macronucleolus. Frequent mitotic figures seen. Few cells show cytoplasmic pigment (arrow). ( Hematoxylin & Eosin, 400 X)

Figure **C**: Tumor cells showing diffuse strong reactivity for S-100 (Immunohistochemistry, DAB- Chromogen, 400 x)

Figure **D**: Tumor cells showing focal however strong and specific reactivity for HMB45 (Immunohistochemistry, DAB- Chromogen, 400 x)