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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Case Series

Case series of genital melanosis and a rare scenario of malignant melanoma arising in the vulval melanosis

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Abstract

Melanosis is the uncommon benign condition characterised by hyperpigmentation of the basal epithelium and extremely rare in female genital tract. Clinically it can mimic as melanoma and differentiating it from malignancy is mandatory to provide appropriate treatment. Though rare mucosal melanosis can turn into malignant melanoma. So biopsy of any pigmented lesion is always indicated prior to determining the need for therapy versus observation. Here we present three cases of female genital tract melanosis out of which two cases are cervical melanosis and one case of vulval melanosis turning into malignant melanoma. Also various pigmented lesions are discussed here. Knowledge of this disease is poor. So this study highlights the need for the biopsy and follow up of pigmented lesions and create awareness among clinicians about this rare case scenario.

Keywords: Melanosis, Female genital tract, Malignant melanoma.

Received: 24-07-2024; **Accepted:** 13-03-2025; **Available Online**: 18-11-2025

1. Introduction

Melanosis is the benign lesion most often discovered by incidental finding on the histopathological examination in which melanin pigment is confined to the basal layer of the squamous epithelium and on visual inspection may have an appearance similar to that of malignant melanoma. Melanosis is relatively common in oral and gastrointestinal tract. It is an uncommon finding in the female genital tract and most reported cases have been in the vulva.[1]

2. Case Presentation

2.1. Case 1

A 40-year-old female presented to gynaecology outpatient department for uterine prolapse. Patient underwent vaginal hysterectomy. On gross examination cervix was hypertrophied, keratinised and everted and showed a blackish brown hyperpigmented areas (**Figure 1** a). No growth or any other abnormality was present. Microscopic examination revealed keratinization of ectocervix with benign pigmented melanocytes in basal layer of epithelium without involving the stroma (**Figure 1** b & c).

2.2. Case 2

A 67 year old female attended gynaecology out patient department for uterine prolapse. On colposcopic examination there was third degree uterovaginal prolapse. Patient underwent vaginal hysterectomy. On gross examination cervix revealed brownish black hyperpigmented flat areas (**Figure 2** a). No growth or any other abnormality was present. Microscopic examination shows mild hyperplasia of ectocervix and basal layer with pigmented melanocytes (**Figure 2** b & c).

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https://doi.org/10.18231/j.ijogr.97687.1763463224

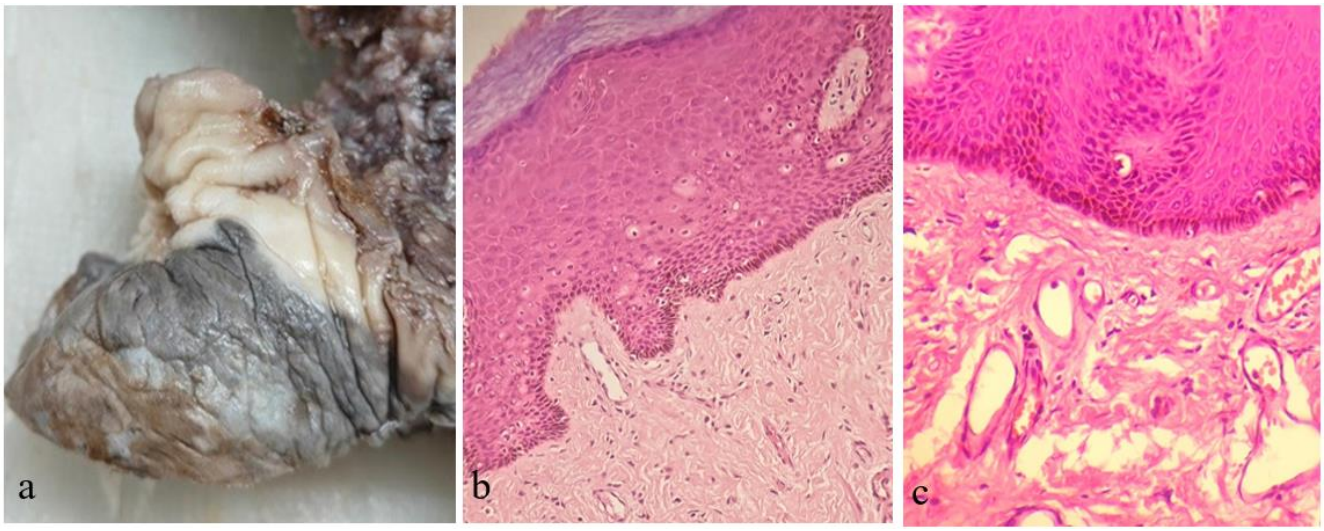

Figure 1: Cervical melanosis. (**a**): Hypertrophied and keratinised cervix shows blackish brown hyperpigmented flat areas. (**b & c**): Photomicrographs show hyperkeratotic stratified squamous epithelium of the uterine cervix with hyperpigmentation of the basal layer. No atypical melanocytes present. (Hematoxylin & Eosin, 10X and 40X)

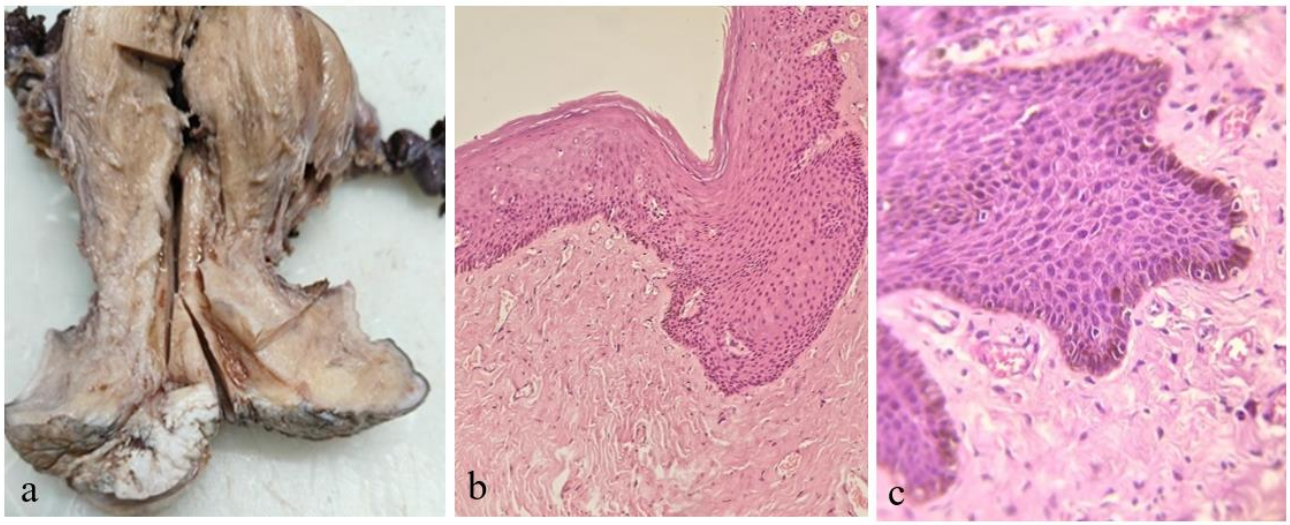

Figure 2: Cervical melanosis. (**a**): Hystrectomy specimen shows keratinised cervix with brownish black hyperpigmented flat areas. (**b & c**): Photomicrographs show cervical epithelium with benign densely pigmented melanocytes in basal layer of epithelium. (Hematoxylin & Eosin, 10X and 40X)

2.3. Case 3

A 52-year-old female presented with complaints of swelling in the labial region for two and a half months, associated with mild discharge. Growth measuring 2×3 cm arising from labia minora showed an irregular ulcerated surface with hyperpigmentation and white patches. Wide local excision done and sent for HPE.

Histopathological examination revealed ulceration with underlying round to oval tumour cells showing pleomorphic and prominent eosinophilic nucleoli and heavily pigmented cytoplasm in sheets, nests and solid islands with delicate fibrous septa. Extensive areas of necrosis with minimal lymphocytic infiltrate noted. Diagnosed as malignant melanoma (**Figure 3** b & c).

Immunohistochemistry of HMB 45 (**Figure 3** d), Melan A (**Figure 3** e), CD117 (**Figure 3** f), & BAP -1 showed positive staining. Adjacent vulval mucosa shows extensive melanosis (**Figure 3** a).

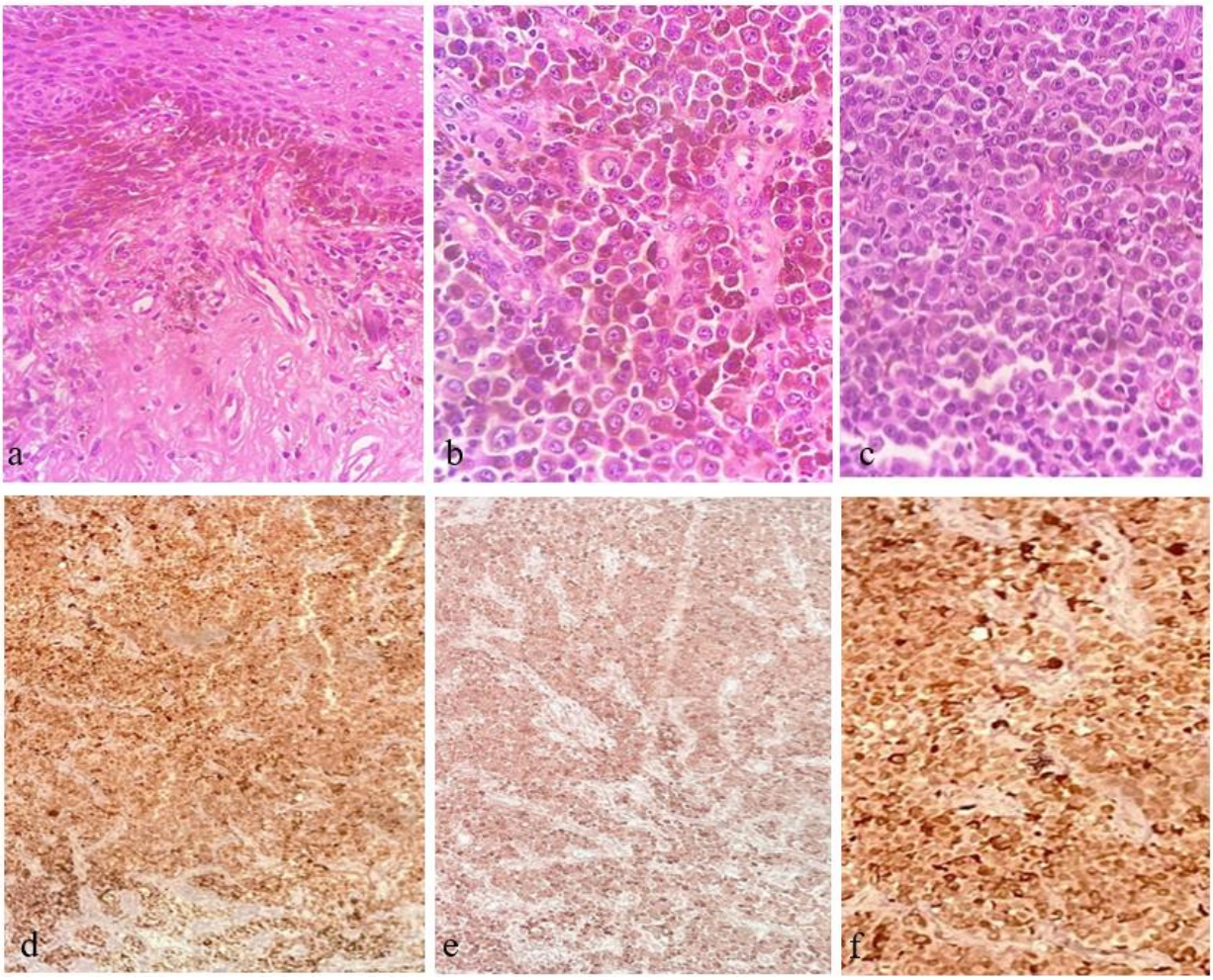

Figure 3: Vulval melanosis with malignant melanoma. **(a):** Melanosis: vulval epithelium with hyperpigmentation of the basal layer (H & E,40X). (**b & c**): Melanoma:Tumor cells arranged in sheets showing pleomorphic, prominent eosinophilic nucleoli and heavily pigmented cytoplasm.(Hematoxylin & Eosin, 40X). **(d, e & f):** Immunohistochemistry: Tumor cells positive for HMB-45, Melan A & CD117

3. Discussion

Melanosis is an uncommon process characterized by hyperpigmentation of the basal epithelium. The criteria used to diagnose the melanosis is benign pigmented melanocytes in basal layer of epithelium and not involving the stroma. Modality of diagnosis is histopathological examination.[2] The etiology is poorly understood. But may represent a metaplastic change in response to chronic irritation or trauma.[2] Other risk factors have been implicated, including; chronic inflammatory disease, viral infection and chemical irritants.[3]

It is usually identified during routine gynecological examination. However, biopsy is mandatory when the colposcopic examination reveals a blackish-brown area, even when the cytology is normal. Biopsy is recommended in order to exclude the diagnostic hypothesis of cervical melanoma.[4]

In case of genital melanosis, the possibility of Laugier Hunziker syndrome (idiopathic mucocutaneous lenticular pigmentation), which is characterized by the presence of genital melanosis associated with melanocytic lesion in the oral cavity, should be excluded.[4] Another possible associations are Mc Cunnie Albright syndrome and Carney complex. Mc Cunnie Albright syndrome exhibits labial and genital pigmentation, but it is often unilateral. The syndrome is also accompanied by precocious puberty in females and fibrous dysplasia. Carney complex, that is associated with pigmented lesions, atrial myxoma and multiple endocrine neoplasia.[5]

Both non melanocytic and melanocytic lesions can lead to genital hyperpigmentation. Most common melanocytic lesion is the blue nevi followed by melanotic macule. Non melanocytic pigmented lesions include endometriosis, haemangioma, haemorrhage in nabothian cysts, granulomatous vasculitis, collection of haemosiderin laden macrophages and multinucleate giant cells surrounding carbon like pigment, giant cell reaction to foreign material.

Melanosis common in 41-50 years age group. Histopathologically melanosis is represented by basal layer

hyperpigmentation of the squamous mucosa with or without increase in number of melanocytes. If number of melanocytes is increased, some authors use the term letingenes. Almost all of the melanosis cases have shown involvement of ectocervix only with an exception showing changes in squamous metaplastic endocervical gland.

The studies show blue nevi is commonest and melanosis is the least common entities with an incidence of 1.2% and 0.05%, respectively. All cases of blue nevi lesions were located in the stroma of the endocervix whereas cervical melanosis were present in the ectocervix.

Blue nevi show presence of melanocytes in endocervical stroma. Three types of blue nevi are described which include stromal melanocyte focus, mixed type and nevoid type based on presence of slender spindled melanocytes, plump spindled melanocytes and nevoid epithelioid stromal melanocytes respectively . Both blue nevi and melanosis show positivity for S100 and melanocytic markers HMB-45 and Melan A. Primary malignant melanomas are distinctive and usually show junctional activity in squamous epithelium with nesting pattern or poorly differentiated lesions with features of anaplasia, high mitotic activity, pigmentation and diffuse strong immunopositivity for S100 and melanocytic markers. It is important to exclude similar lesions elsewhere in body to label it as primary melanoma.[6]

Benign pigmented lesions of the vulva include vulvar melanosis; lentigo simplex; junctional nevi, compound nevi, intradermal nevi, dysplastic nevi, seborrheic keratosis and acanthosis nigricans. Pigmented vulvar neoplasia may include Paget's disease, vulvar intraepithelial neoplasia, squamous carcinoma and melanoma. Clinical examination, histopathological and immunohistochemical studies may be helpful in making the differential diagnosis. Melanomas are commonly immunoreactive for S-100 protein and HMB-45.[7]

Nearly 10% of women will have a pigmented vulval lesion in her lifetime. Vulvar melanosis is a condition characterized by pigmented lesion that may mimic malignant melanoma clinically. Pigmented lesions on mucous membranes and anogenital skin should be biopsied .Even though vulvar melanosis has a benign prognosis, differential diagnosis should be considered including tumors such as basal cell carcinoma and melanoma where an early diagnosis is important.[8]

Melanoma of the vulva and vagina comprise less than < 2% of melanoma in women. Vulval melanoma is a rare gynaecological condition 2 to 10% of all primary vulvar malignancies. Vulval melanoma is the second most common histological type after squamous-cell carcinoma of the vulva. Vulva is the most common site of melanoma in the female genital tract, even though Vulval Melanoma is a rare melanoma (1–2% of all melanomas) and only 0.2% of 100,000 women per year will be diagnosed. It primarily affects white women in the fifth to eighth decade. The Mean age at diagnosis is 60–63 years. Commonest site of involvement as follows: Labia majora and labia minora > periclitoral / clitoris > midline structures (e.g., periurethral, introitus and posterior fourchette). Histological types are Lentiginous (most common), Superficial spreading (less common), Nodular and pagetoid (rare). Molecular profile of vulval melanoma different from cutaneous and mucosal melanoma. Genetic profile revealed C-KIT followed by NRAS and BRAF mutation rarely found. C-KIT mutation is more common in mucosal melanoma as compare to cutaneous melanoma. Further studies are required to understand the outcomes and role of immunotherapy between the different mutations.[3]

Main treatment for vulval melanoma is the surgery along with radiotherapy, chemotherapy, cytokine treatment .In recent years immune check point inhibitors and target therapies plays vital role. The role of surgery in vulval melanoma remains the same. Wide local excision is considered a better treatment option. Negative margin distance is correlated with the Breslow thickness for invasive melanoma. When the Breslow thickness is <1 mm, the negative margin distance is 1 cm; when it is 1.01 -2 mm, the negative margin distance is 1-2 cm; when it is >2 mm, negative margin distance is 2 cm. When nodal metastasis present, complete lymph node dissection is performed.[9] Vulval melanoma is a radio-resistant tumor. It is indicated only for inoperable advanced patients or patients with post-operative recurrence. Chemotherapy is considered only for immune check point inhibitors and target therapy resistant tumors. Ipilimumab, human monoclonal antibody can block CTLA-4 and enhance antitumor effects as a single agent or combination agent. Nivolumab is the anti-PD1 antibody under phase III trial. The results showed that nivolumab is more effective than ipilimumab. However, combination therapy with nivolumab+ ipilimumab resulted in better response.[10] The primary malignant vulvar melanoma and extragenital cutaneous melanoma show similar behaviour. However, some studies have shown that the general prognosis of patients with vulvar melanoma is worse than that of women with extragenital melanoma and SCC of the vulva, showing a greater tendency for local and distal recurrence.[11]

4. Conclusion

This study emphasis the rarity of genital hyperpigmentation and majority of them are benign nature, however a careful microscopic examination will help to differentiate between various pigmented lesions ranging from non-melanocytic lesions to harmless benign melanosis to melanomas. A biopsy of any pigmented lesion is indicated prior to determining the need for therapy versus observation.

Long term follow up studies showed vulval melanosis not progressed to malignant melanoma. However is exceptionally rare, melanosis can turn into malignant melanoma. It suggests that mucosal melanosis is a possible precursor of melanoma. Vulval melanoma in the setting of

mucosal melanosis is rare with the poor outcome and knowledge of this disease is poor. Overall it has different genetic and molecular profiles which made challenges to treat. These tumors will harbor an activating mutations and may respond to targeted agents. So mutational analysis and newer targeted therapy related trials are encouraged to improve the quality of life.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Raghavan V, Pandurangan P. Case series of genital melanosis and a rare scenario of malignant melanoma arising in the vulval melanosis. *Indian J Obstet Gynecol Res*. 2025;12(4):785–789.