REVIEW
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Genital Pigmented Lesions

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Abstract

The genital region is the crossroad of the skin, reproductive and urinary system. In patients with genital skin lesions, the collaboration of urologists and dermatologists is frequent and this alleviates distress, anxiety and even hidden fears of patients, especially in genital pigmented lesions. differential diagnosis of genital pigmented lesions has a wide range spectrum like melanosis, melanocytic nevi, seborrheic keratosis, basal cell carcinoma, other diseases such as post-inflammatory hyperpigmentation, lichen planus, Bowen's disease, Bowenoid papulosis and most importantly melanoma. In approach to solitary or multiple pigmented lesions; dermoscopy is a non-invasive tool that captures clues which cannot be seen by naked-eye and provides guidance for unnecessary biopsies or surgery for dermatologists. This review intends to provide a dermatological approach and aspects for urologists in the differential diagnosis of pigmented lesions on the genital area in female and male patients.

Keywords: Genital pigmented lesions, melanoma, melanosis

Introduction

The genital region is the crossroad of three organ systems: Skin, reproductive and urinary system. Many patients are concerned and mostly fear that their genital skin lesion is either a sexually transmitting disease or a cancer. Urologists and gynecologists are at the forefront of the physicians consulted when genital lesions are concerned. The diagnosis of these lesions and managing patients with concerns about their genital region or genital disease takes skill and expertise but can be mastered with practice and with collaboration of different specialists (1).

The description of the genital region can be confusing dermatologically, histologically and anatomically. The lips, oral cavity, perianal region, penile and vulval genital areas are considered mucosal regions. In a comparison of mucosal regions and other skin areas; pigmented and non-pigmented lesions are rare in mucosal regions and due to that fact also published data and clinical knowledge are limited. The male genital region has less mucosal component compared with the female genital region. The anatomical and histological differences in male and female genital regions, such as the transition of mucosa and skin, glandular differences, follicular and non-follicular areas, make a regular recognizable lesions that are located on other parts of body sites, difficult to diagnose in the genital region, especially in women. Furthermore, mucosal or skin located pigmented genital lesions-with blue, brown, black appearance is less recognizable by the naked eye and for this reason they need additional diagnostic tools (2). In the differentiation of pigmented lesions from melanomas in the genital region, dermoscopy is a non-invasive tool that provides clues about skin structures in epidermis, dermo-epidermal junction and dermis.

Pigmented skin lesions in the genital area include melanosis, melanocytic nevi, seborrheic keratosis, basal cell carcinoma (BCC), other diseases such as post-inflammatory hyperpigmentation, lichen planus, Bowen disease, Bowenoid papulosis and most importantly melanoma. The population-based incidence of pigmented lesions is approximately 10-20% (3). According to the abovementioned facts, dermatology consultation of a patients with skin lesions in this specific region (including mucosal and non-mucosal areas) is frequent for suspected cases (4). Urologists should be able to perform patient and lesion-oriented evaluation together in the diagnosis and treatment of pigmented genital lesions. While patient-oriented data such as the patient's age, skin type, etc. gain importance when separating the preliminary diagnoses and making a biopsy or treatment

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decision, consideration of the lesion's shape, structure, color symmetry and changes in the follow-up are important among the lesion-oriented data. This review intends to provide a dermatological aspect for urologists in the differential diagnosis of pigmented lesions on the genital area in female and male patients.

Genital Melanosis

Melanosis (lentiginosis) can occur in both in genital and oral mucosa and genital melanosis (genital lentiginosis, mucosal melanosis) is an infrequent and benign condition. Despite its benign behavior, genital melanosis can clinically mimic melanoma. It is discrete, hyperpigmented macules or patches on genitalia and histopathologically, the number of melanocytes is normal, but there is increased basal layer hyperpigmentation with lack of melanocytic hyperplasia (5). In other body parts most solar lentigines occur in fair-skinned individuals and are induced by exposure ultraviolet light exposure, but the etiology of genital melanosis is unknown. The estimated incidence is approximately 0.01% (5,6). In patients with syndromes like Laugier-Hunziker and Peutz-Jeghers mucosal melanosis can be diagnosed in high frequencies and in patients with inflammatory skin diseases like lichen planus genital melanosis have been reported (5,7-9). They occur in both sexes especially in darker skin-colored individuals and the onset occurs in the fourth decade in most of the patients. Genital melanosis lesions are asymptomatic, multiple or solitary brown or black macules (Figures 1,2). They frequently remain stable or enlarge slowly (5,10). In doubtful cases, the distinction from melanoma depends on the age of occurrence, clinical findings, clinical and dermoscopic follow-up. Dermoscopically; parallel, structureless, reticular, ring-like patterns and several subtype patterns are described (11,12). In clinically suspected lesions which are characterized by asymmetry, irregular borders, multifocality, variegated pigmentary patterns and large size, biopsy is usually necessary to exclude melanoma. In large lesions shave or incisional, in small lesions, punch or excisional biopsy can be adequate depending on the suspicion. No treatment is necessary in the diagnosis of genital melanosis. Even though they are not considered premalignant lesions, long-term clinical and dermoscopic follow-up of lesions is recommended (5,10). However, in another study, Haugh et al. (10) pointed out that in patients with a history of cutaneous melanoma genital melanosis was increased in number and they recommend in patients with genital melanosis total body skin examinations for the possibility of melanoma in any body site.

Melanocytic Nevi

Melanocytic nevi are congenital or acquired collection of melanocytes. In terms of location; melanocytic nevi such as compound, junctional and blue nevi, that are located in the genital region have a very low percentage of melanocytic nevi in the whole body (Figures 3-5). Melanocytic nevi in the genital region is frequently located on the labium major, minor, clitoris and glans penis (13-15). Melanocytic nevi are included in the differential diagnosis of melanosis and melanoma and

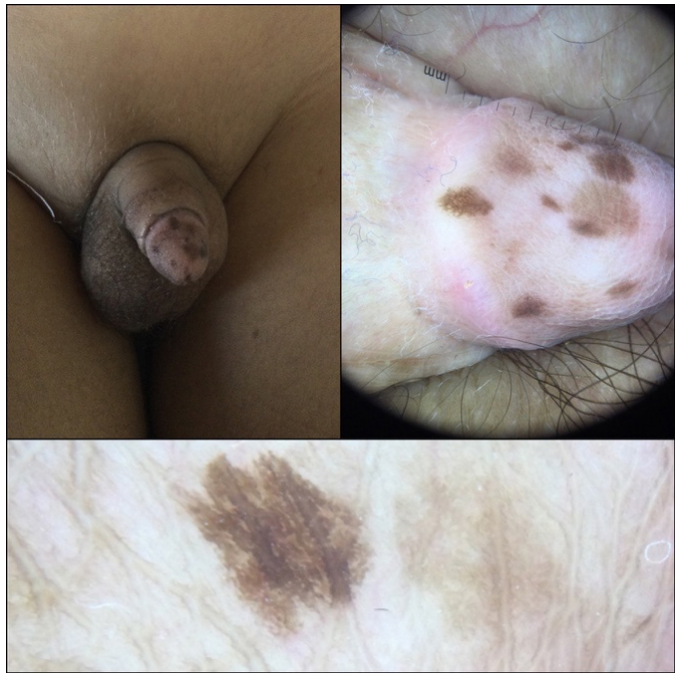

Figure 1. Sixteen-year-old male patient with genital melanosis-multiple, dark-brown, light-brown, different in size, regular shaped macules and patches located on glans penis. Dermoscopic image shows reticular and hyphal pattern

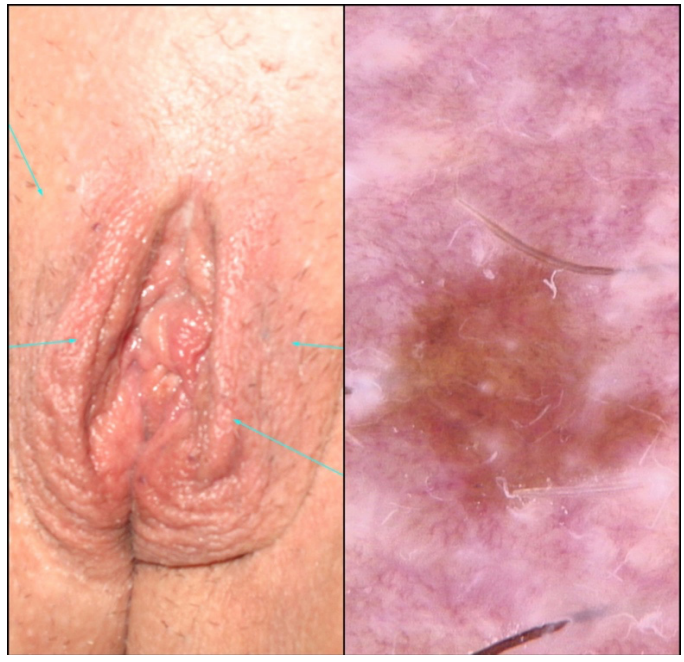

Figure 2. Forty-two-year-old female patient with one-month history of genital melanosis-a millimetric, regular bordered, hyperpigmented macule located on labium major. Dermoscopic image shows structureless and ring-like pattern

are often detected in younger patients. They are common in fairer-skinned individuals. In most cases, melanocytic nevi are detected solitary, often 0.5-1 cm in size. They can be flat macules, papules slightly raised from the skin, or nodular, and are asymmetrical lesions that may change in color from brown to gray (13-15). There is no evidence that melanocytic nevi of the genital skin have a greater risk of malignant transformation than those in other anatomical sites. In the last decade; it has become increasingly clear that benign melanocytic nevi on certain areas of the body, such as the scalp, flexural areas, genital area, needs special attention. Because to their nature exhibit unusual histopathological features, they can also clinically mimic dysplastic nevi and melanoma (16). This is a major concern for melanocytic nevi in young, premenopausal women, located in the vulvar region and there is an increased risk of over-diagnosing melanoma clinically and histopathologically (3,16). But because of lack of evidence, clinical and dermoscopic follow-up is recommended for genital melanocytic nevi. It has been reported that dermoscopically genital melanocytic nevi often exhibit a regular pigment network, but sometimes suspicious criteria such as atypical black network structure, irregular radial structure and irregular globules can be seen (14). However, eruptive multiple blue nevi, characterized by dermoscopically diffuse homogeneous gray-blue pigmentation in the penile region, were reported, but it was also emphasized that a possible melanoma metastasis could not be excluded without biopsy (17). Excisional biopsy is the preferred method for lesions that have melanoma in differential diagnosis, but in cases with glans penis localization, punch biopsy can be performed from the most dermoscopically suspected area of the lesion (18).

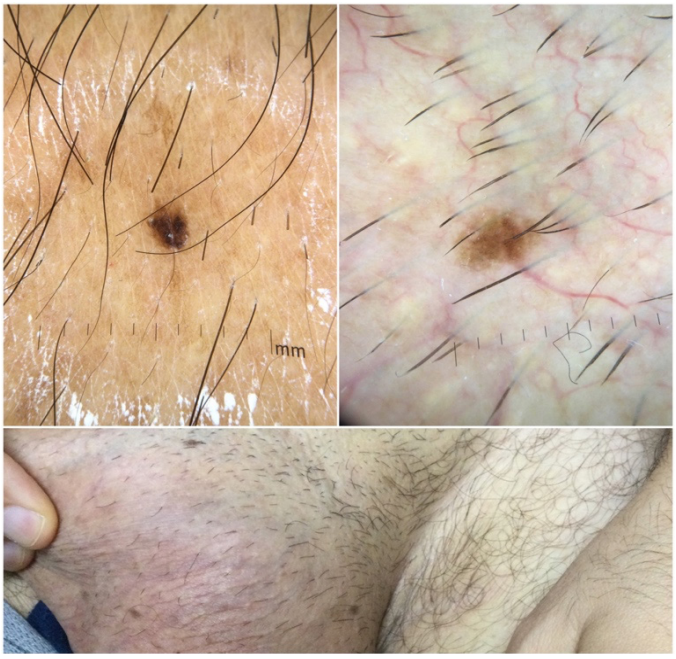

Figure 3. Thirty-five-year-old male patient with two melanocytic nevi-0.5 cm diameter, black and dark-brown, irregular shaped papules on scrotum. Dermoscopic images-(left) symmetrical globular pattern, (right) homogeneous structureless pattern

Seborrheic Keratosis

Seborrheic keratosis is one of a common benign keratocytic tumor, especially in fair skinned individuals. The main etiology

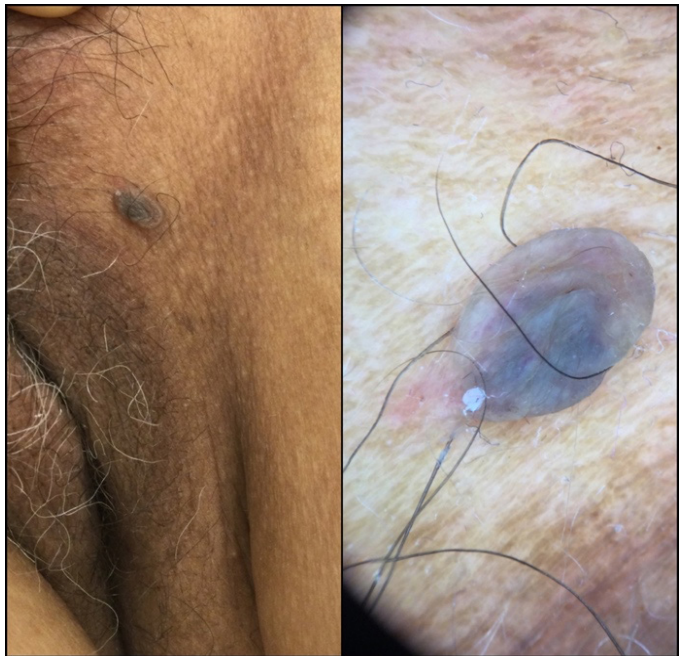

Figure 4. Forty-eight-year-old male patient with intradermal nevi-0.4 cm diameter, pedunculated, dark grey-brown papule. Dermoscopic images shows- comma vessels and homogenous bluish structureless areas

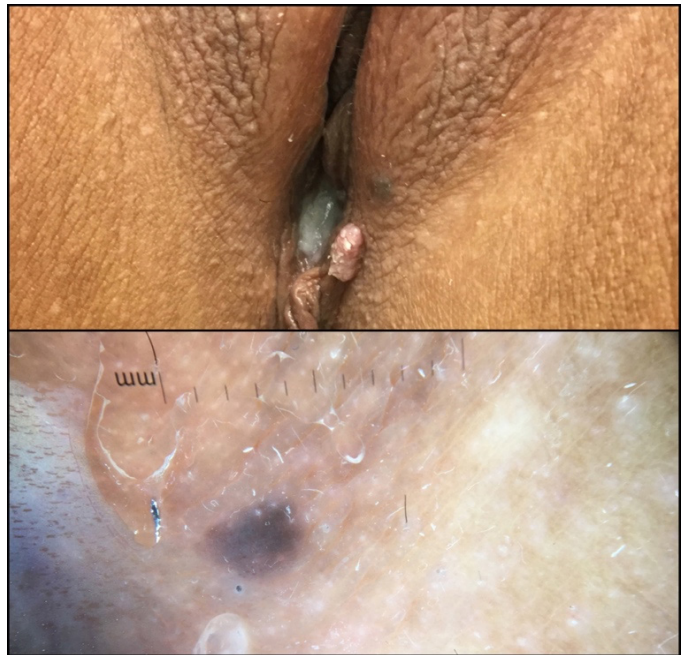

Figure 5. Twenty-eight-year-old female patient with blue nevi-0.5 mm, blue-black, regular bordered papule on labium major. Dermoscopic image shows homogenous pattern

is unknown, but genetic and environmental factors have been reported in some studies (19-23). The role of the human papilloma virus is controversial in etiology, sun exposure is a well-known factor, but it can also be diagnosed in sun-protected areas such as the genital region (19,24-26). It occurs on non-mucosal area of the genital region. The most frequent localization was the penile shaft. Seborrheic keratosis is frequent in middle age patients and increases in number by the age. Clinically; they vary in color-pink to black and they are asymptomatic, solitary, well-defined, waxy papules, plaques and nodules (Figure 6). They can mimic condyloma acuminata, pigmented BCC, bowenoid papulosis and melanoma and in some cases, clinical diagnosis is not easy (19-23). There are well-known dermoscopic features such as milia-like cysts, comedo-like openings, cerebriform appearance and mouth-eaten borders (27,28). In the lack of demonstrative dermoscopic appearance, shave or punch biopsy is necessary to distinguish other malignities that are mentioned above histopathologically (20-22). Treatment is usually unnecessary but due to patient-oriented cosmetic concerns and symptoms like pruritus, electrocauterization, cryosurgery and ablative treatments such as trichloroacetic aside, laser can be performed.

Basal Cell Carcinoma

BCC is the most common skin cancer all around the world (29). Ultraviolet exposure is considered a primary factor in pathogenesis, but 20% of lesions are located in non-sun exposed areas (30,31). In sun-protected areas such as genital region BCC is extremely rare and etiology of genital BCC is unknown. As with other body part localizations, genital BCC is diagnosed in elderly patients. The sex predominancy is unclear for genital BCC (32). The most frequent localization in women is labium majus whereas in men scrotum (33). All subtypes of BCC, such as nodular, morpheic, pigmented can be observed in the genital region. The most frequent subtype of BCC in the genital region is the nodular type same as non-genital BCCs (32). The usual clinical presentation is skin colored, plaque or nodules with elevated borders and telangiectasias. Pigmented BCC is a subtype with hyperpigmented plaque and nodules and resembles melanoma (Figure 7) (34). Dermoscopically, there are well-known criteria in diagnosis of BCC, such as arborising vessels, leaf-like brown, black areas, blue-grey ovoid nests with the absence of a pigment network. Most BCCs are local invasive and rarely metastasize (35). Because of lack of early diagnosis due to privacy of the genital region and misdiagnosis of initial lesions; genital BCC cases are frequently are large in diagnosis (32). Even it is rare metastasis of BCC in the genital area has been reported (36). In a cohort study; penile BCCs showed poorer prognosis than the scrotum (32). The treatment of choice is surgery, for relapsing cases, Mohs microsurgery is recommended. In cases of inoperability, radiotherapy, imiquimod, 5-flourouracil, photodynamic and target treatment for the hedgehog pathway can be other options for treatment (37). treatment, follow-up is recommended for 5 years (38).

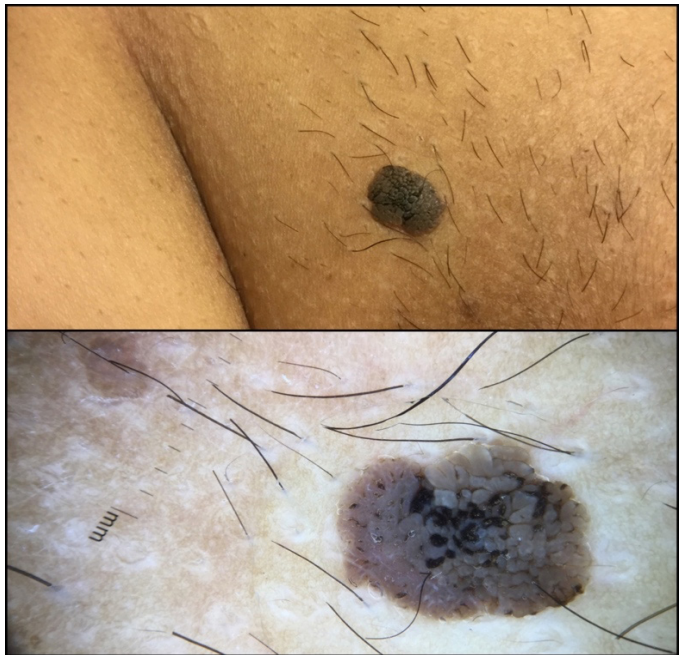

Figure 6. Forty-three-year-old male patient with seborrheic keratosis-1 cm diameter black vegetative plaque. Dermoscopic image shows cerebriform structures, comedo-like openings

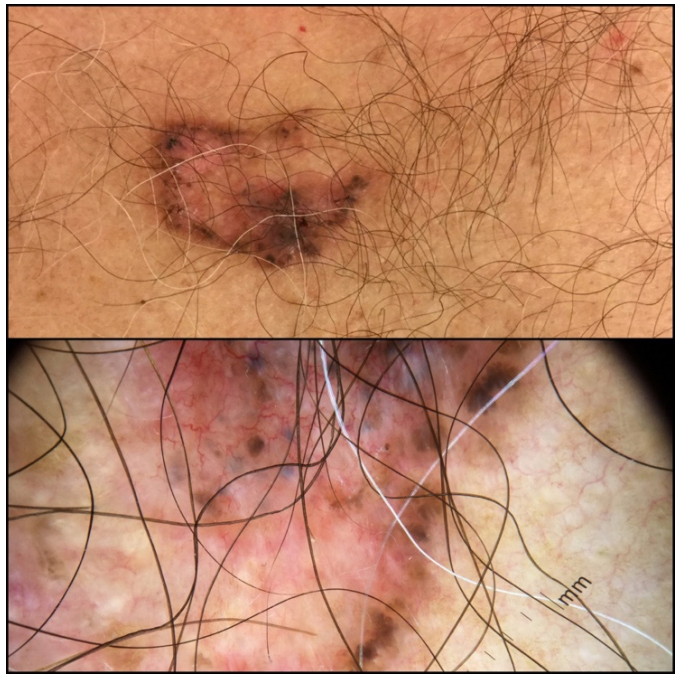

Figure 7. Fifty-two-year-old male patient with pigmented basal cell carcinoma on pubic region- 3 cm diameter, irregular shaped with elevated border, multicolored hyperpigmented plaque. Dermoscopic image shows arborizing vessels, maple-leaf structures

Other Diseases

Post-inflammatory hyperpigmentation in the genital region may occur after inflammation by previous diseases such as contact dermatitis (Figure 8), lichen planus (Figure 9), lichen sclerosus, trauma, burn, infections etc. (39-41). The color may vary from light tan to gray, blue, brown, or black. In diagnosis; history of patient is important rather than biopsy. Treatment depends on the primary inflammatory disease.

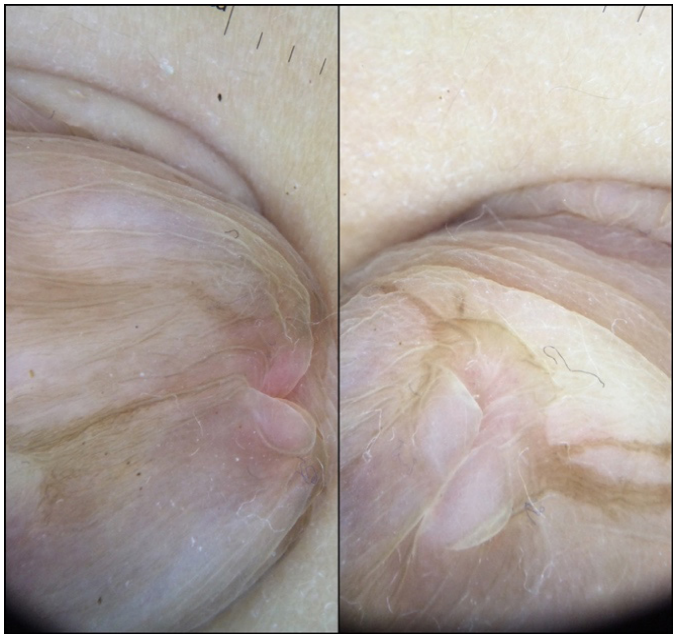

Figure 8. Nine-year-old male patient with post-inflammatory hyperpigmentation after irritant contact dermatitis with death nettle solution. Dermoscopic image shows linear brown blotches

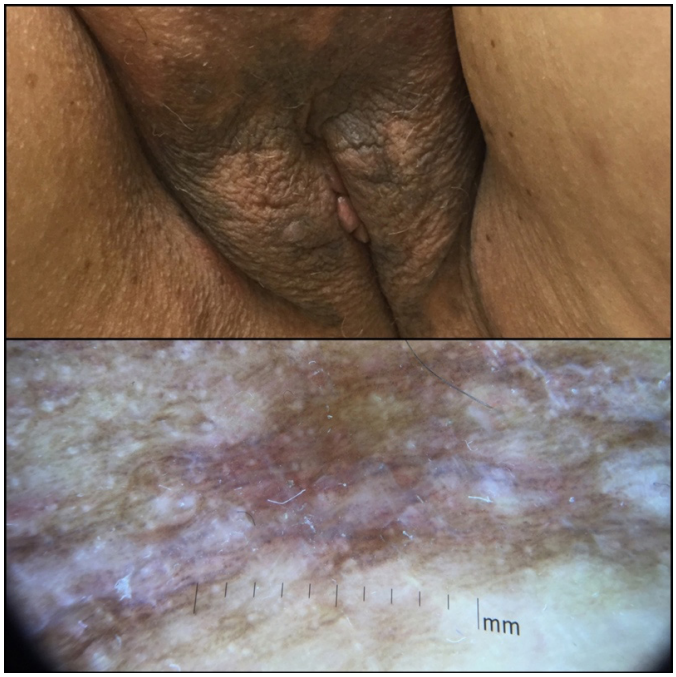

Figure 9. Fifty-two-year-old female patient with lichen planus-hyperpigmented plaque on genital area, including pubic region, labium major, minor and vagina. Dermoscopic image shows white lines and perifollicular hyperpigmentation

Bowen's disease is a frequent skin colored, erythematous, solitary plaque that increases in size and is histopathologically known as carcinoma *in situ* (41). Squamous cell carcinoma may arise in about 5% of Bowen's disease cases (42). Pigmented Bowen's disease is a rare subtype and clinically mimics pigmented BCC and melanoma (43,44). Treatment options are excision, CO_2 laser therapy, cryosurgery, topical imiquimod, 5-FU creams and there is no optimum treatment strategy (41).

Bowenoid papulosis is an intraepithelial neoplasia that etiologically related especially to oncogenic high-risk types of human papillomavirus. Multiple hyperpigmented papules and plaques on the anogenital region are a clinical presentation of Bowenoid papulosis (41,45). In the differential diagnosis of vascular lesions, melanosis, pigmented BCC, melanoma and Bowenoid papulosis, dermoscopy is a useful tool compared with naked-eye (46-48). Therapeutic options include local destructive methods such as cryosurgery, electrocauterization, laser therapy etc. (41,45).

Melanoma

Genital melanoma (Figure 10), is an extremely rare malignancy. Vulvar melanomas are 1% of all melanomas and approximately

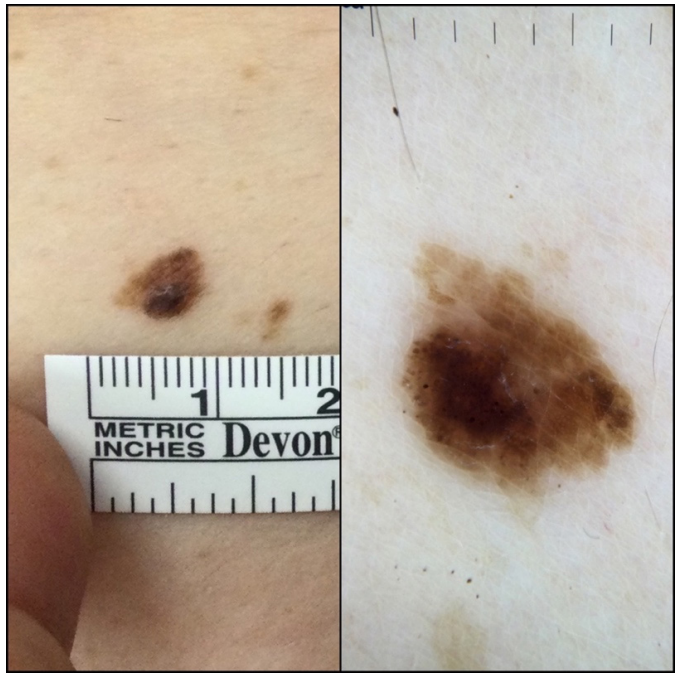

Figure 10. Sixty-three-year-old female patient with melanoma (Breslow: 0.83 mm) on pubic region-irregular shaped, multi-colored, 0.7 mm diameter maculopapular lesion. Dermoscopic image shows bilateral peripheral blotches, atypical globules, atypical vascularization

200 primary penile melanoma cases have been described in the literature that reflects less than 0.1% of primary melanomas (49-51). The common age-onset of both vulvar and penile melanoma is that they both affect elderly individuals from the sixth and seventh decades of life (51,52). It is a necessity to point out that; while distinguishing melanoma and other pigmented lesions in the genital region, the age-onset is one of the most important data from the history of patient. Ultraviolet light is a risk factor for cutaneous melanoma, but there is no sufficient data for genital melanoma. Recent studies indicate that while cutaneous melanomas frequently carry BRAF (serine/threonine kinase) mutations, mucosal melanomas carry mutations or extra copies of KIT (receptor tyrosine kinase) and rarely have BRAF mutations (53-55). Clinically; irregular bordered, single or multi-colored (more than 2: Light-brown, dark-brown, black, blue, gray, red, white), asymmetrical, ulcerated macule, papule, plaques or nodules can be seen. Dermoscopically well-known criteria for non-mucosal melanoma are atypical network, atypical globules, blue-white veil, pseudopods, radial streaming, atypical vascularization, focal sharply cut-off borders, and mucosal melanoma additionally color and structureless area (56,57). Multidisciplinary approach gives chance to early diagnosis. The histopathological features have greater value for staging and due to that fact, excisional biopsy is the ideal approach to suspicion of melanoma (49-52). Depending on the size and site of the lesion, punch, biopsy can be performed (49-52). Treatment for localized melanoma is surgical excision. In cutaneous melanoma, the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend surgical margins depending on tumor thickness (based on category I evidence): 0.5-1 cm for melanoma *in situ*, 1 cm for invasive melanoma with a Breslow's thickness ≤1 mm, 1-2 cm for Breslow 1.01-2 mm, and 2 cm for Breslow >2 mm. In accordance with the National Comprehensive Cancer Network guidelines, margins may be modified to accommodate individual anatomic or functional considerations. The prognosis of vulval, vaginal and penile melanoma is very poor (49,51,58). Because multiple primary melanoma cases in follow-up of melanoma patient there is expert work groups recommend at least annually dermatological follow-up, ranging from 3 to 12 months based on risks such as family history, atypical mole syndrome, a number of atypical nevi (59,60).

Conclusion

Genital pigmented lesions have a wide range spectrum of diseases. The diagnosis of genital pigmented lesions and managing these patients require multidisciplinary expertise but can be mastered with practice. Besides this; patient self-awareness should be increased, especially when follow-up is carried out in patients with known genital pigmented lesion. When pigmented genital lesions are encountered in the urological examination, the patient's advanced age, the existing or the new and rapidly growing lesions that show asymmetry in shape, color and structure may require biopsy indication. In cases that melanoma is among the preliminary diagnoses and excisional biopsy cannot be performed, it may help approach an accurate diagnosis that dermatologists and urologists determine the biopsy region together while biopsy is taken from a histopathologically appropriate part of the lesion. Generally, it is recommended that urologists should take excisional biopsies because it is a surgically challenging area. The management and approach of these lesions should be tailor-made and need to be organized in a multidisciplinary fashion because of the features that make the genital region special to other body parts.

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