Vulvar nevi, melanosis, and melanoma: An epidemiologic, clinical, and histopathologic review

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Pigmented vulvar lesions are present in approximately 1 in 10 women and include melanocytic and nonmelanocytic proliferations. Vulvar nevi, melanosis, and melanoma are particularly challenging because of the similarity of their clinical and/or histopathological presentation. As a result, they are often difficult to diagnose, may result in patient and physician anxiety, and can lead to unneeded, potentially disfiguring surgical procedures. Because it is often detected late, vulvar melanoma carries a poor prognosis with associated significant morbidity and mortality, underscoring the importance of prompt recognition and treatment. In this review, we analyze the distinct epidemiologic, clinical, and histopathologic characteristics of vulvar nevi, melanosis, and melanoma, discuss treatment options, and propose a practical, systematic approach to facilitate formulation of a differential diagnosis and initiation of appropriate management. (J Am Acad Dermatol 2014;71:1241-9.)

Key words: dermoscopy; melanocytic nevi; melanoma; melanosis; pigmented lesions; reflectance confocal microscopy; vulvar region.

Pigmented vulvar lesions are estimated to occur in 10% to 12% of women.[1,2] The differential diagnosis includes benign and malignant melanocytic proliferations, such as nevi and melanoma. Nonmelanocytic proliferations such as basal cell carcinoma, squamous cell carcinoma, vascular tumors, seborrheic keratosis, and condylomata acuminata can also present as pigmented vulvar lesions.[3,4] Other nonhyperproliferative entities marked by increased pigmentation include melanosis, postinflammatory and physiologic hyperpigmentation, and acanthosis nigricans.[3,4]

Because of overlapping clinical and histologic features between malignant and benign processes, pigmented vulvar lesions often pose a diagnostic challenge. As such, they may be a source of patient and physician anxiety and can result in unnecessary surgical procedures. Although rare, vulvar melanoma is often diagnosed late and carries a poor prognosis; early identification and intervention may improve patient outcomes. Despite the potential importance of early diagnosis, a survey revealed that only 4% of dermatologists examined the vulvar region in patients presenting for an annual examination.[5]

This review summarizes the distinguishing epidemiologic, clinical, and histopathologic characteristics of vulvar nevi, melanosis, and melanoma. We include dermoscopy and reflectance confocal microscopy as noninvasive imaging techniques that may aid in the diagnosis of pigmented vulvar lesions. We also evaluate the prognosis of these vulvar lesions and propose a practical approach to their management.

VULVAR NEVI

Epidemiology and pathogenesis

Approximately 2% of adult females have vulvar nevi, accounting for 23% of all pigmented vulvar lesions.[1,2] In addition, there exists a small subset of nevi termed "atypical melanocytic nevi of the genital type" (AMNGT), which represent approximately 5% of vulvar nevi.[6,7]

Vulvar nevi may present during childhood. A chart review of 1159 patients with a diagnosis of

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"nevus" seen at our center revealed a prevalence of genital nevi of approximately 3.3% in girls younger than 18 years.[8] In adults, vulvar nevi are generally found in premenopausal women. Common vulvar nevi are associated with a median age of 28 to 33 years, whereas AMNGT are associated with a younger age of 17 to 26 years.[2,6,9,10]

Clinical presentation

Common vulvar nevi (Fig 1) present as symmetric macules and flat-topped or dome-shaped papules, ranging in color from pink to dark brown-black, or rarely, blue.[2,3,7] Common nevi are well-demarcated with regular borders, uniform pigmentation, and diameter typically less than 1 cm.[3,4,8,9,11] They are most often located on the labia majora, labia minora, and clitoral hood.[2]

CAPSULE SUMMARY

- Vulvar nevi, melanosis, and melanoma represent pigmented vulvar lesions that are often difficult to diagnose.
- This review article presents the distinguishing epidemiologic, clinical, and histopathologic characteristics of these lesions and proposes an approach to their diagnosis and management.
- Patient age and clinical presentation can guide initial management.

Compared with common vulvar nevi, AMNGT are more frequently located on the labia minora[9] and have an equal distribution between mucosal surfaces and hair-bearing skin of the external genitalia in adults.[10] In children younger than 10 years, AMNGT have a strong predilection for mucosal sites.[7,10,12,13] AMNGT may have alarming clinical features, such as dark pigmentation, irregular borders, and large size.[10] In addition, a personal or family history of dysplastic nevi or melanoma may be found at increased rates in patients with AMNGT.[10,12]

Dermoscopy

Dermoscopy may assist in the diagnosis of vulvar nevi. Globular and homogeneous patterns predominate among common vulvar nevi.[8,9,14,15] In AMNGT, a mixed pattern, defined as the combination of 2 or more dermoscopic patterns, has been observed most frequently.[9] The globular and homogenous patterns constituted the other most detected morphologies.[9]

Histopathology

Common vulvar nevi exhibit regularly sized, evenly distributed nests of melanocytes, which show no cytologic atypia[16] (Fig 2). AMNGT may have a more alarming histopathologic presentation with features overlapping with those of melanoma.[12,13] Findings include confluent nests of atypical melanocytes irregularly distributed along the epidermal rete ridges, focal pagetoid spread, adnexal involvement, loss of cellular cohesion giving a pseudovascular appearance, dermal fibrosis, and inflammation.[6,7,10,13,17,18] Characteristics that distinguish AMNGT from melanoma are the presence of dermal maturation, rare mitotic activity, and lack of cell necrosis and ulceration[7] (Table I). Vulvar nevi with concurrent changes of lichen sclerosus pose an additional diagnostic challenge as they can demonstrate a lichenoid lymphocytic infiltrate and melanophages with pigment incontinence that may mimic features of melanoma regression.[19]

Prognosis and management

Vulvar nevi are believed to follow a benign clinical course.[11] There is conflicting evidence regarding the presence of vulvar nevi as risk markers for vulvar melanoma. One series of 219 Swedish females found pre-existing nevi adjacent to 35% of vulvar melanomas arising in the hairy skin of the external genitalia.[20,21] In contrast, among 157 vulvar melanomas arising on mucosal surfaces or at the hairy-mucosal junction, 98% occurred de novo, ie, lacking an associated nevus.[21] AMNGT are also believed to have low malignant potential as demonstrated by 2 studies including 36 and 56 AMNGT, respectively.[10,12] None of these nearly 100 lesions showed evidence of malignant transformation over a 15- to 16-year period.[10,12] One lesion recurred 1.5 years after an initial biopsy specimen that had positive margins. Upon re-excision, this lesion was noted to be a nevus with mild atypia.[10] As with nevi at other sites,[22] it is unclear whether it is necessary to achieve clear biopsy specimen margins. Close observation of all biopsy sites for evidence of repigmentation should be considered during routine skin and gynecologic examinations. Similarly, it is prudent to periodically examine vulvar nevi for any changing features that might prompt concern for the development of melanoma.

VULVAR MELANOSIS

Epidemiology and pathogenesis

Vulvar melanosis, also referred to as vulvar lentiginosis and vulvar melanotic macules, represents approximately 68% of pigmented vulvar lesions in reproductive-aged women.[1] Vulvar melanosis is more commonly found among perimenopausal women with a median age of 40 to 44 years.[2,9] When arising in children, the

Fig 1. Vulvar compound melanocytic nevus, clinical presentation. Typical flat-topped, uniformly brown papule with well-defined, regular borders located at the hairy-glabrous junction in a 29-year-old woman.

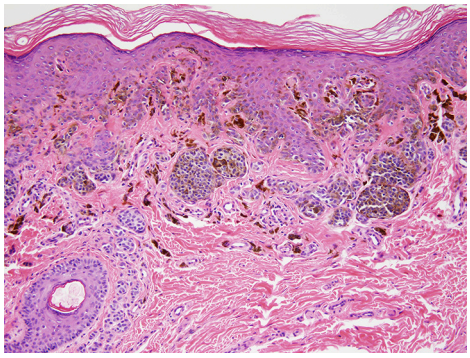

Fig 2. Vulvar compound melanocytic nevus, histopathologic presentation. There is a proliferation of small, uniform melanocytes arranged as single units and small nests at the dermoepidermal junction and within the papillary dermis. Melanocytes at the base of the nevus extend along a follicle. (Hematoxylin-eosin stain; original magnification: ×20.)

multisystem genodermatoses should be considered[3,4,23-27] (Table II).

The pathogenesis of vulvar melanosis is largely unknown. Based on case reports, authors have speculated on the possible relationship between melanosis and hormonal factors, as there are descriptions of the onset of melanosis after oral contraceptive use and in the immediate postpartum period.[28-30] Other cases have associated melanosis with lichen sclerosus[19] and infection with human papillomavirus (HPV).[31] A study of 23 cases of vulvar melanosis, however, was unable to detect the presence of any of the most common HPV types within lesions.[32]

Clinical presentation

Vulvar melanosis presents as single or multiple, asymmetric macules or patches with variable shades of tan to black color, irregular and poorly demarcated borders, and varying size[3,4] (Fig 3). Vulvar melanosis has a predilection for the mucosal surfaces rather than keratinized, hair-bearing skin of the external genitalia.[3] The labia minora is the most commonly affected site, although the labia majora can also be involved.[2,3,30,33]

Dermoscopy and reflectance confocal microscopy

Dermoscopy may aid in minimizing unnecessary biopsy specimens of vulvar melanosis. In the largest study of vulvar melanosis to date, 6 dermoscopic patterns were observed among 71 patients.[34] The most frequently detected pattern, occurring in 32% of lesions, was a ringlike pattern.[34] Other common morphologies include homogeneous, globular-like, parallel, cobblestone, and reticular-like patterns.[15,34-36]

Reflectance confocal microscopy may be used to facilitate the diagnosis of vulvar melanosis. One study found that the cells around the papillae appeared more refractive in vulvar melanosis lesions compared with unaffected vulvar mucosa.[37] In another analysis of 12 lesions, a ringed or draped pattern with polycyclic papillae was reported.[38]

Histopathology

Major findings of vulvar melanosis are increased melanin in the basal layer and a normal or slightly increased number of melanocytes arranged as single units at the dermoepidermal junction[14,29] (Fig 4 and Table I). Other possible features include elongation of the rete ridges, dendritic melanocytes at the dermoepidermal junction, and melanophages in the papillary dermis.[3,16,39]

Prognosis and management

Vulvar melanosis typically follows a benign clinical course.[39] Two follow-up studies of vulvar melanosis lesions over a period of 2 to 14 years demonstrated minimal clinical change and no malignant transformation.[29,40] Whether vulvar melanosis is a risk factor for the development of melanoma remains poorly understood. One series studying patients with HPV infection discovered melanosis adjacent to half of vulvar melanoma cases.[41] It is unclear, however, whether the melanosis was associated with melanoma development or concurrent infection with HPV.[41]

Clinical follow-up, together with baseline photography and sequential imaging, is a conservative management approach that can be used in some patients with vulvar melanosis[3] (Fig 5). Biopsy should be considered if the distinction between melanosis and melanoma cannot be made on clinical

Table I. Key histopathologic differences among vulvar nevi, melanosis, and melanoma

	Vulvar nevi	AMNGT	Vulvar melanosis	Vulvar melanoma
Increased basal melanin	−	−	+	−
Pagetoid spread	−	+/− (Focal)	−	++ (Prominent)
Cytologic atypia	−	+/− (Superficial)	−	++ (Deep)
Dermal maturation	+	+	−	−
Mitoses	−	+/− (Rare, superficial)	−	++ (Prominent, both superficial and deep)
Necrosis	−	−	−	++
Ulceration	−	−	−	++

Data from Brenn.[18]
AMNGT, Atypical melanocytic nevi of the genital type.

Table II. Genodermatoses that may be associated with vulvar melanosis

Genodermatosis	Sites of melanosis	Other key features	Genetic mutation
Peutz-Jeghers syndrome	Lips, oral mucosa, nostrils, perianal area, hands and feet, genitalia	Gastrointestinal hamartomatous polyps, increased risk of breast, ovarian, pancreatic, and gastrointestinal cancers	STK11
Carney complex	Lips, eyelids, conjunctiva, oral mucosa, genitalia	Myxomas (especially cardiac), endocrine tumors, psammomatous melanotic schwannoma, blue nevus	PRKAR1A
LEOPARD syndrome (multiple lentigines syndrome)	Face, neck, trunk, genitalia	Electrocardiographic abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, sensorineural deafness	PTPN11, RAF1, BRAF
Bannayan-Riley-Ruvalcaba syndrome	Face, genitalia	Macrocephaly, intestinal hamartomatous polyposis, lipomas, hemangiomas, intellectual disability, gross motor deficiencies, joint hyperextensibility, pectus excavatum, scoliosis	PTEN
Dowling-Degos disease	Axillae, groin, flexural folds (knees, elbows, wrists, under the breasts), neck, genitalia	Reticulated hyperpigmentation, follicular papules, comedone-like lesions, perioral scars, hypopigmented or erythematous macules	KRT5

grounds or if a lesion is noted to have changed over time. Of note, there exists a report of an 80-year-old woman presenting with what appeared to be extensive vulvar melanosis. Multiple biopsy specimens, however, showed evidence of vulvar melanoma invasive to 15 mm.[42] As vulvar melanosis is rare in women of advanced age, this case indicates the need for biopsy to investigate the possibility of melanoma in cases clinically resembling new-onset melanosis.

VULVAR MELANOMA

Epidemiology and pathogenesis

Vulvar melanoma is the second most common malignancy of the vulva after squamous cell carcinoma, accounting for approximately 10% of vulvar malignancies.[43] A population-based study from Sweden found that 2.6% of melanomas occurred in the vulvar region. Interestingly, 2% of all melanomas in females occur on the vulvar mucosa, yet this site

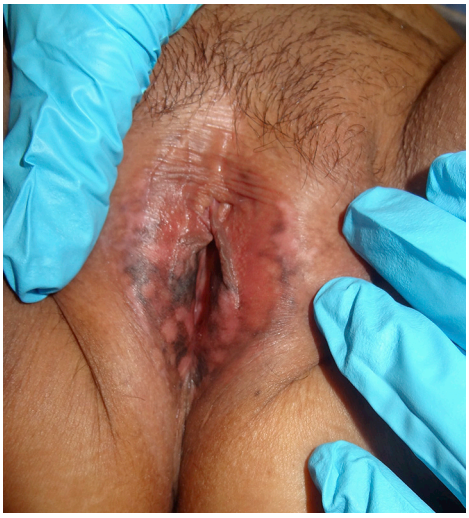

Fig 3. Vulvar melanosis, clinical presentation. Multiple dark brown to black macules with irregular borders arranged in a reticular-like pattern distributed throughout the labia minora and vulvar vestibule in a 51-year-old woman.

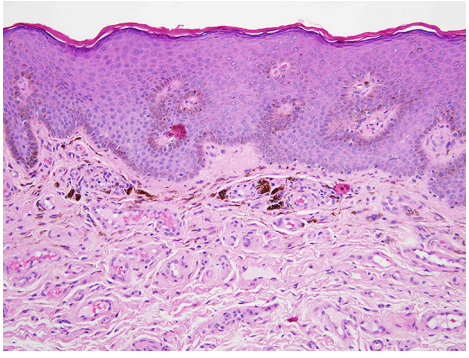

Fig 4. Vulvar melanosis, histopathologic presentation. An increased number of small, uniform melanocytes arranged as single units can be seen at the dermoepidermal junction. Basal layer hyperpigmentation and superficial melanophages are evident. (Hematoxylin-eosin stain; original magnification: ×20.)

accounts for 0.7% of total body surface area.[21] Affected women are generally Caucasian and in the fifth to eighth decades of life.[44-46] Compared with cutaneous melanoma, vulvar melanoma has a less marked difference in incidence across racial-ethnic groups.[47,48]

The cause of vulvar melanoma is complex and multifactorial. From a molecular genetic perspective, vulvar melanomas more closely resemble acral lentiginous rather than cutaneous melanoma. Chromosomal copy number alterations, particularly in 1q and 6p, may be present at increased rates compared with cutaneous melanomas.[20] KIT is the most commonly mutated gene with sequence variants detected in up to 35% of vulvar melanomas.[44] More rarely, NRAS and BRAF mutations have been described.[49,50] Chronic inflammation, such as from lichen sclerosus, has been linked to vulvar melanoma; however, these findings are somewhat controversial.[51-54] Infection with HPV subtypes has also been identified in vulvar melanoma, but its role in pathogenesis remains unclear.[41,55]

Unlike most cutaneous melanomas, ultraviolet radiation does not appear to play a significant causal role in the pathogenesis of vulvar melanoma.[4] First, vulvar melanoma incidence rates have been observed to increase from south to north in the United States.[48,56] Second, the vulvar region is not commonly exposed to ultraviolet radiation. There is a single case report, however, of a vulvar melanoma with a Breslow thickness of 5.4 mm arising in a 24-year-old woman with extended indoor tanning bed use.[57]

Clinical presentation

Vulvar melanoma (Fig 6) may present as macules, papules, or nodules of irregular coloration, asymmetric borders, and diameter larger than 7 mm.[3,4,21] Amelanotic lesions may also be encountered. In a 25-year study of 219 Swedish females, amelanotic "reddish" polyps were the most frequently observed clinical manifestations of vulvar melanoma.[21] Accompanying nonspecific symptoms can include vulvar bleeding, pruritus, discharge, irritation, or lymphadenopathy.[20] Primary vulvar melanoma most frequently develops on the labia majora, followed by the labia minora and clitoral hood.[20] Roughly half of vulvar melanomas arise on glabrous (mucosal) skin, 38% at the hairy-glabrous skin junction, and 13% on hairy skin of the external genitalia.[20]

Dermoscopy and reflectance confocal microscopy

Dermoscopy may facilitate the early identification of vulvar melanoma. In an observational analysis of 11 mucosal melanomas, including 2 vulvar melanomas, the dermoscopic combination of blue, gray, or white color plus structureless zones was highly predictive of melanoma.[58] Other studies observed findings similar to cutaneous melanoma, including a multicomponent pattern composed of irregular dots and globules, multiple colors, a blue-white veil, and atypical vessels.[9,15,59]

Reflectance confocal microscopy may be used in the detection of vulvar and other mucosal melanomas. Distinct characteristics of mucosal melanomas include: (1) architectural atypia, consisting of a high density of dendritic cells, pagetoid cells, and melanocytes arranged in sheets and nests; and

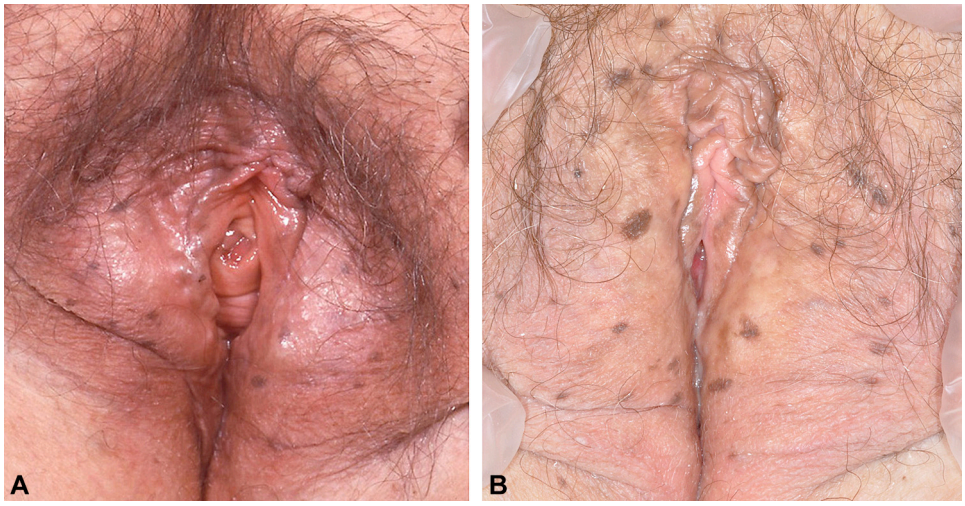

Fig 5. Pigmented vulvar lesions, follow-up with sequential imaging. **A**, Initial photograph of pigmented vulvar lesions in a 64-year-old woman. Although biopsy specimen was never obtained, these lesions were clinically diagnosed as benign, likely representing vulvar melanosis. **B**, Follow-up image 7 years later demonstrating stability of these lesions. The oval brown macule on the medial aspect of the right labia is partially obscured by folded skin in **A**.

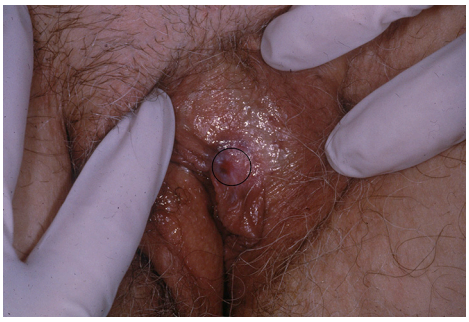

Fig 6. Vulvar melanoma, clinical presentation. Blue-white nodule with focal ulceration (circled in black) in a 75-year-old woman with a history of cutaneous malignant melanoma in situ.

(2) cytologic atypia, characterized by large, pleomorphic shape, bright cytoplasm, and a hyporefractive nucleus.[37,38]

Histopathology

Many vulvar melanomas are of the mucosal lentiginous subtype, but can also be of the superficial spreading or nodular subtypes, especially on keratinized surfaces.[21] Atypical melanocytes arranged as confluent nests and sheets, prominent pagetoid spread, and absent dermal maturation are typically seen (Table I). Ulceration, cell necrosis, and abundant and reticular dermal mitoses are often present.

Prognosis and management

Vulvar melanomas are often diagnosed late and carry a poor prognosis, with a mean 5-year survival ranging from 27% to 60%.[20] Breslow thickness, ulceration, and lymph node involvement are important prognostic indicators.[20,45,48,60] In addition, older patients generally have worse outcomes.[45,48] Similarly, African Americans had decreased survival in some series[48,60]; this may be a result of more advanced disease at presentation.[61]

If vulvar melanoma is suspected, a biopsy specimen that includes as much of the lesion as possible, ensuring adequate depth for staging purposes, is warranted.[4] In tumors thicker than 1 mm, examination of lymph nodes is generally recommended.[4] Treatment is largely surgical.[20] In patients with localized disease, there appears to be no significant difference in tumor-specific survival among those undergoing radical vulvectomy compared with more conservative surgery such as a wide local excision.[45,47] With the advent of molecularly targeted and immune therapies, such as imatinib, a small molecule inhibitor of KIT, there exist promising new treatment modalities that may improve the care and outcomes of patients with vulvar melanoma.[62,63]

APPROACH TO THE PATIENT WITH POSSIBLE VULVAR NEVI, MELANOSIS, OR MELANOMA

When encountering pigmented vulvar lesions that are clinically suspicious for nevi, melanosis, or melanoma, a systematic approach may aid the formulation of a differential diagnosis (Fig 7). For example, in children and young women, macules and papules less than 1 cm in diameter are likely to be common melanocytic nevi or AMNGT. Such

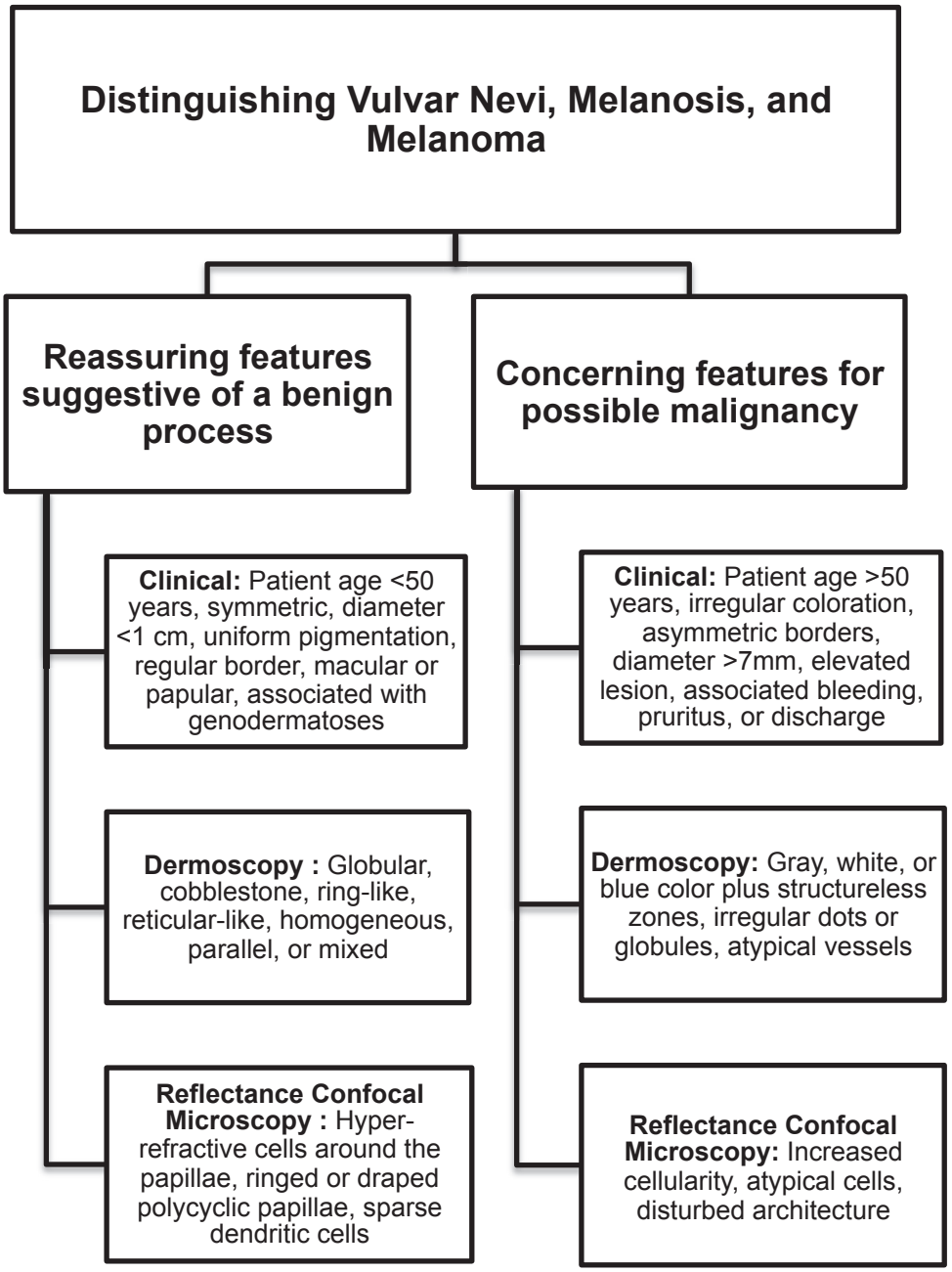

Fig 7. An approach to patients with possible vulvar nevi, melanosis, or melanoma.

lesions should be followed up during routine skin and gynecologic examinations for any signs of changing features.

In middle-aged women or children with genodermatoses, single or multifocal macules or patches displaying color variegation and irregular borders may represent vulvar melanosis. Follow-up using sequential imaging can be used. In lesions clinically indistinguishable from melanoma, biopsy should be considered. Although studies have reported using dermoscopy and reflectance confocal microscopy on pigmented lesions of the vulvar region, this can be a difficult area to examine and may require specialized equipment and proper hygienic measures, such as antibacterial gel or translucent wrap overlying the instrument's optical window.[15]

As vulvar melanoma is more common in older patients, when encountering raised lesions or new-onset melanosis in women older than 50 years, melanoma must be high on the differential diagnosis. In addition, in women of any age, associated pruritus, bleeding, discharge, discomfort, lymphadenopathy, or ulceration should raise concern for possible melanoma. In such instances, a biopsy that provides

adequate depth ascertainment should be performed as soon as possible.

Conclusion

Pigmented lesions of the vulva can pose a diagnostic challenge. Understanding the distinct epidemiologic, clinical, and histopathologic characteristics of vulvar nevi, melanosis, and melanoma can facilitate appropriate patient treatment. Although the risk of transformation of benign lesions into melanoma is low, maintaining a high level of suspicion is necessary given the aggressive clinical course of vulvar melanoma. It is important that dermatologists evaluate the vulvar region during routine skin cancer screening examinations, inquiring about any new or changing lesions, examining the area as appropriate, and instructing patients to undergo regular gynecologic surveillance.

REFERENCES

1. Rock B, Hood AF, Rock JA. Prospective study of vulvar nevi. J Am Acad Dermatol 1990;22:104-6.
2. Rock B. Pigmented lesions of the vulva. Dermatol Clin 1992; 10:361-70.
3. Edwards L. Pigmented vulvar lesions. Dermatol Ther 2010;23: 449-57.
4. Venkatesan A. Pigmented lesions of the vulva. Dermatol Clin 2010;28:795-805.
5. Krathen MS, Liu C, Loo DS. Vulvar melanoma: a missed opportunity for early intervention? J Am Acad Dermatol 2012;66:697-8.
6. Ribé A. Melanocytic lesions of the genital area with attention given to atypical genital nevi. J Cutan Pathol 2008;35(Suppl): 24-7.
7. Christensen WN, Friedman KJ, Woodruff JD, Hood AF. Histologic characteristics of vulvar nevocellular nevi. J Cutan Pathol 1987;14:87-91.
8. Hunt RD, Orlow SJ, Schaffer JV. Genital melanocytic nevi in children: experience in a pediatric dermatology practice. J Am Acad Dermatol 2014;70:429-34.
9. Ferrari A, Zalaudek I, Argenziano G, Buccini P, De Simone P, Silipo V, et al. Dermoscopy of pigmented lesions of the vulva: a retrospective morphological study. Dermatology 2011;222: 157-66.
10. Gleason BC, Hirsch MS, Nucci MR, Schmidt BA, Zembowicz A, Mihm MC, et al. Atypical genital nevi: a clinicopathologic analysis of 56 cases. Am J Surg Pathol 2008;32:51-7.
11. Elder DE. Precursor to melanoma and their mimics: nevi of special sites. Mod Pathol 2006;19(Suppl):S4-20.
12. Clark WH, Hood AF, Tucker MA, Jampel RM. Atypical melanocytic nevi of the genital type with a discussion of reciprocal parenchymal-stromal interactions in the biology of neoplasia. Hum Pathol 1998;29(Suppl):S1-24.
13. Friedman RWJ, Ackerman AB. Difficulties in the histologic diagnosis of melanocytic nevi on the vulvae of premenopausal women. In: Ackerman AB, editor. Pathology of malignant melanoma. New York (NY): Masson; 1981. pp. 119-27.
14. Virgili A, Zampino MR, Marzola A, Corazza M. Vulvar melanocytic nevi: a dermoscopic investigation. Dermatology 2010;221:55-62.
15. Ronger-Savle S, Julien V, Duru G, Raudrant D, Dalle S, Thomas L. Features of pigmented vulval lesions on dermoscopy. Br J Dermatol 2011;164:54-61.
16. Heller DS. Pigmented vulvar lesions—a pathology review of lesions that are not melanoma. J Low Genit Tract Dis 2013;17: 320-5.
17. Hosler GA, Moresi JM, Barrett TL. Nevi with site-related atypia: a review of melanocytic nevi with atypical histologic features based on anatomic site. J Cutan Pathol 2008;35: 889-98.
18. Brenn T. Atypical genital nevus. Arch Pathol Lab Med 2011; 135:317-20.
19. El Shabrawi-Caelen L, Soyer HP, Schaeppi H, Cerroni L, Schirren CG, Rudolph C, et al. Genital lentigines and melanocytic nevi with superimposed lichen sclerosus: a diagnostic challenge. J Am Acad Dermatol 2004;50:690-4.
20. Ragnarsson-Olding BK. Primary malignant melanoma of the vulva—an aggressive tumor for modeling the genesis of non-UV light-associated melanomas. Acta Oncol 2004;43:421-35.
21. Ragnarsson-Olding BK, Kanter-Lewensohn LR, Lagerlöf B, Nilsson BR, Ringborg UK. Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: clinical observations and histopathologic features. Cancer 1999;86:1273-84.
22. Hocker TL, Alikhan A, Comfere NI, Peters MS. Favorable long-term outcomes in patients with histologically dysplastic nevi that approach a specimen border. J Am Acad Dermatol 2013;68:545-51.
23. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 2010;59: 975-86.
24. Stratakis CA, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab 2001;86:4041-6.
25. Sarkozy A, Digilio MC, Dallapiccola B. LEOPARD syndrome. Orphanet J Rare Dis 2008;3:13.
26. Gorlin RJ, Cohen MM Jr, Condon LM, Burke BA. Bannayan-Riley-Ruvalcaba syndrome. Am J Med Genet 1992;44:307-14.
27. Batycka-Baran A, Baran W, Hryncewicz-Gwozdz A, Burgdorf W. Dowling-Degos disease: case report and review of the literature. Dermatology 2010;220:254-8.
28. Barnhill RL, Albert LS, Shama SK, Goldenhersh MA, Rhodes AR, Sober AJ. Genital lentiginosis: a clinical and histopathologic study. J Am Acad Dermatol 1990;22:453-60.
29. Sison-Torre EQ, Ackerman AB. Melanosis of the vulva: a clinical simulator of malignant melanoma. Am J Dermatopathol 1985;7(Suppl):51-60.
30. Rudolph RI. Vulvar melanosis. J Am Acad Dermatol 1990;23: 982-4.
31. Núñez-Troconis J, Delgado M, González G, Rivas A, Molero K. Melanosis of the vagina and human papillomavirus infection, an uncommon pathology: case report. Invest Clin 2011;52: 268-73.
32. Jih DM, Elder DE, Elenitsas R. A histopathologic evaluation of vulvar melanosis. Arch Dermatol 1999;135:857-8.
33. Karney MY, Cassidy MS, Zahn CM, Snyder RR. Melanosis of the vagina: a case report. J Reprod Med 2001; 46:389-91.
34. Ferrari A, Buccini P, Covello R, De Simone P, Silipo V, Mariani G, et al. The ringlike pattern in vulvar melanosis: a new dermoscopic clue for diagnosis. Arch Dermatol 2008;144:1030-4.
35. Mannone F, De Giorgi V, Cattaneo A, Massi D, De Magnis A, Carli P. Dermoscopic features of mucosal melanosis. Dermatol Surg 2004;30:1118-23.

36. Carli P, De Giorgi V, Cattaneo A, Giannotti B. Mucosal melanosis clinically mimicking malignant melanoma: non-invasive analysis by epiluminescence microscopy. Eur J Dermatol 1996;6:434-6.
37. Cinotti E, Perrot JL, Labeille B, Adegbidi H, Cambazard F. Reflectance confocal microscopy for the diagnosis of vulvar melanoma and melanosis: preliminary results. Dermatol Surg 2012;38:1962-7.
38. Debarbieux S, Perrot JL, Erfan N, Ronger-Savle S, Labeille B, Cinotti E, et al. Reflectance confocal microscopy of mucosal pigmented macules: a review of 56 cases including 10 macular melanoma. Br J Dermatol 2014;170:1276-84.
39. Maize JC. Mucosal melanosis. Dermatol Clin 1988;6:283-93.
40. Lenane P, Keane CO, Connell BO, Loughlin SO, Powell FC. Genital melanotic macules: clinical, histologic, immunohistochemical, and ultrastructural features. J Am Acad Dermatol 2000;42:640-4.
41. Rohwedder A, Slominski A, Wolff M, Kredentser D, Carlson JA. Epidermodysplasia verruciformis and cutaneous human papillomavirus DNA, but not genital human papillomavirus DNAs, are frequently detected in vulvar and vaginal melanoma. Am J Dermatopathol 2007;29:13-7.
42. Kerley SW, Blute ML, Keeney GL. Multifocal malignant melanoma arising in vesicovaginal melanosis. Arch Pathol Lab Med 1991;115:950-2.
43. Moxley KM, Fader AN, Rose PG, Case AS, Mutch DG, Berry E, et al. Malignant melanoma of the vulva: an extension of cutaneous melanoma? Gynecol Oncol 2011;122:612-7.
44. Rogers GS, Gibson LE. Mucosal, genital, and unusual clinical variants of melanoma. Mayo Clin Proc 1997;72:362-6.
45. Sugiyama VE, Chan JK, Shin JY, Berek JS, Osann K, Kapp DS. Vulvar melanoma: a multivariable analysis of 644 patients. Obstet Gynecol 2007;110:296-301.
46. Irvin WP, Legallo RL, Stoler MH, Rice LW, Taylor PT, Anderson WA. Vulvar melanoma: a retrospective analysis and literature review. Gynecol Oncol 2001;83:457-65.
47. Hu DN, Yu GP, McCormick SA. Population-based incidence of vulvar and vaginal melanoma in various races and ethnic groups with comparisons to other site-specific melanomas. Melanoma Res 2010;20:153-8.
48. Weinstock MA. Malignant melanoma of the vulva and vagina in the United States: patterns of incidence and population-based estimates of survival. Am J Obstet Gynecol 1994;171:1225-30.
49. Aulmann S, Sinn HP, Penzel R, Gilks CB, Schott S, Hassel JC, et al. Comparison of molecular abnormalities in vulvar and vaginal melanomas. Mod Pathol doi:10.1038/modpathol.2013.211. Published online March 7, 2014.
50. Omholt K, Grafström E, Kanter-Lewenson L, Hansson J, Ragnarsson-Olding BK. KIT pathway alterations in mucosal melanomas of the vulva and other sites. Clin Cancer Res 2011;17:3933-42.
51. Carlson JA, Mu XC, Slominski A, Weismann K, Crowson AN, Malfetano J, et al. Melanocytic proliferations associated with lichen sclerosus. Arch Dermatol 2002;138:77-87.
52. Hassanein AM, Mrstik ME, Hardt NS, Morgan LA, Wilkinson EJ. Malignant melanoma associated with lichen sclerosus in the vulva of a 10-year-old. Pediatr Dermatol 2004;21:473-6.
53. Rosamilia LL, Schwartz JL, Lowe L, Gruber SB, Quint EH, Johnson TM, et al. Vulvar melanoma in a 10-year-old girl in association with lichen sclerosus. J Am Acad Dermatol 2006;54(Suppl):S52-3.
54. Schaffer JV, Orlow SJ. Melanocytic proliferations in the setting of vulvar lichen sclerosus: diagnostic considerations. Pediatr Dermatol 2005;22:276-8.
55. Rohwedder A, Philips B, Malfetano J, Kredentser D, Carlson JA. Vulvar malignant melanoma associated with human papillomavirus DNA: report of two cases and review of literature. Am J Dermatopathol 2002;24:230-40.
56. Moan J, Porojnicu AC, Dahlback A, Grant WB, Juzeniene A. Where the sun does not shine: is sunshine protective against melanoma of the vulva? J Photochem Photobiol B 2010;101:179-83.
57. Pawelec M, Karmowski A, Karmowski M. A rare case of vulvar melanoma in a young woman who frequently tanned in tanning parlors. Arch Dermatol 2010;146:347-8.
58. Blum A, Simionescu O, Argenziano G. Dermoscopy of pigmented lesions of the mucosa and the mucocutaneous junction: results of a multicenter study by the International Dermoscopy Society (IDS). Arch Dermatol 2011;147:1181-7.
59. Lin J, Koga H, Takata M, Saida T. Dermoscopy of pigmented lesions on mucocutaneous junction and mucous membrane. Br J Dermatol 2009;161:1255-61.
60. Mert I, Semaan A, Winer I, Morris RT, Ali-Fehmi R. Vulvar/vaginal melanoma: an updated surveillance epidemiology and end results database review, comparison with cutaneous melanoma and significance of racial disparities. Int J Gynecol Cancer 2013;23:1118-25.
61. Bellows CF, Belafsky P, Fortgang IS, Beech DJ. Melanoma in African-Americans: trends in biological behavior and clinical characteristics over two decades. J Surg Oncol 2001;78:10-6.
62. Postow MA, Hamid O, Carvajal RD. Mucosal melanoma: pathogenesis, clinical behavior, and management. Curr Oncol Rep 2012;14:441-8.
63. Postow MA, Carvajal RD. Therapeutic implications of KIT in melanoma. Cancer J 2012;18:137-41.