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

Era Caterina Murzaku, BS, Lauren A. Penn, MD, Christopher S. Hale, MD, Miriam Keltz Pomeranz, MD, and David Polsky, MD, PhD

New York, New York

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 keratoses, 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...
“nevus” seen at our center revealed a prevalence of genital nevi of approximately 3.3% in girls younger than 18 years. 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.

Clinical presentation
Common vulvar nevi (Fig 1) present as symmetric, mucosal sites and flat-topped or dome-shaped papules, ranging in color from pink to dark brown-black, or rarely, blue. Common nevi are well-demarcated with regular borders, uniform pigmentation, and diameter typically less than 1 cm. They are most often located on the labia majora, labia minora, and clitoral hood. Compared with common vulvar nevi, AMNGT are more frequently located on the labia minora and have an equal distribution between mucosal surfaces or at the hairy-mucosal junction, 98% of vulvar melanomas arise in these locations.

Histopathology
Common vulvar nevi exhibit regularly sized, evenly distributed nests of melanocytes, which show no cytologic atypia. AMNGT may have a more alarming histopathologic presentation with features overlapping with those of melanoma. 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. Characteristics that distinguish AMNGT from melanoma are the presence of dermal maturation, rare mitotic activity, and lack of cell necrosis and ulceration (Table 1). Vulvar nevi with concurrent changes of lichen sclerosus may pose an additional diagnostic challenge as they can demonstrate a lichenoid lymphocytic infiltrate and melanophages with pigment incontinence that may mimic features of melanoma.

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

Prognosis and management
Vulvar nevi are believed to follow a benign clinical course. There is conflicting evidence regarding the prevalence 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. 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. AMNGT are also believed to have low malignant potential as demonstrated by 2 studies including 36 and 56 AMNGT, respectively. None of these nearly 100 lesions showed evidence of malignant transformation over a 15- to 16-year period. 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. As with nevi at other sites, 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. Vulvar melanosis is more commonly found among perimenopausal women with a median age of 40 to 44 years. When arising in children, the
multisystem genodermatoses should be considered.

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. Other cases have associated melanosis with lichen sclerosus and infection with human papillomavirus (HPV). 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.

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 (Fig 3). Vulvar melanosis has a predilection for the mucosal surfaces rather than keratinized, hair-bearing skin of the external genitalia. The labia minora is the most commonly affected site, although the labia majora can also be involved.

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. The most frequently detected pattern, occurring in 32% of lesions, was a ringlike pattern. Other common morphologies include homogeneous, globular-like, parallel, cobblestone, and reticular-like patterns.

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. In another analysis of 12 lesions, a ringed or draped pattern with polycyclic papillae was reported.

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. Other possible features include elongation of the rete ridges, dendritic melanocytes at the dermoepidermal junction, and melanophages in the papillary dermis.

Prognosis and management
Vulvar melanosis typically follows a benign clinical course. Two follow-up studies of vulvar melanosis lesions over a period of 2 to 14 years demonstrated minimal clinical change and no malignant transformation. 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. It is unclear, however, whether the melanosis was associated with melanoma development or concurrent infection with HPV.

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 (Fig 5). Biopsy should be considered if the distinction between melanosis and melanoma cannot be made on clinical
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. 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. 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

| Table I. Key histopathologic differences among vulvar nevi, melanosis, and melanoma |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Increased basal melanin                      | Vulvar nevi                                   | AMNGT                                        | Vulvar melanosis                              |
| Pagetoid spread                               | -                                             | +/- (Focal)                                  | -                                             |
| Cytologic atypia                              | -                                             | +/- (Superficial)                            | -                                             |
| Dermal maturation                             | +                                             |                                            | -                                             |
| Mitoses                                       | -                                             | +/- (Rare, superficial)                      | + + (Prominent)                               |
| Necrosis                                      | -                                             | -                                            | + +                                            |
| Ulceration                                    | -                                             | -                                            | + +                                            |

Data from Brenn. 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 |

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accounts for 0.7% of total body surface area. Affected women are generally Caucasian and in the fifth to eighth decades of life.

Compared with cutaneous melanoma, vulvar melanoma has a less marked difference in incidence across racial-ethnic groups. 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. KIT is the most commonly mutated gene with sequence variants detected in up to 35% of vulvar melanomas. More rarely, NRAS and BRAF mutations have been described. Chronic inflammation, such as from lichen sclerosus, has been linked to vulvar melanoma; however, these findings are somewhat controversial. Infection with HPV subtypes has also been identified in vulvar melanoma, but its role in pathogenesis remains unclear.

Unlike most cutaneous melanomas, ultraviolet radiation does not appear to play a significant causal role in the pathogenesis of vulvar melanoma. First, vulvar melanoma incidence rates have been observed to increase from south to north in the United States. 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.

Clinical presentation
Vulvar melanoma (Fig 6) may present as macules, papules, or nodules of irregular coloration, asymmetric borders, and diameter larger than 7 mm. 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. Accompanying nonspecific symptoms can include vulvar bleeding, pruritus, discharge, irritation, or lymphadenopathy. Primary vulvar melanoma most frequently develops on the labia majora, followed by the labia minora and clitoral hood. 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.

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. 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. 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
(2) cytologic atypia, characterized by large, pleomorphic shape, bright cytoplasm, and a hyporeflective nucleus.  

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.  

Atypical melanocytes arranged as confluent nests and sheets, prominent pagetoid spread, and absent dermal maturation are typically seen (Table 1). 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%.  

Breslow thickness, ulceration, and lymph node involvement are important prognostic indicators.  

In addition, older patients generally have worse outcomes.  

Similarly, African Americans had decreased survival in some series; this may be a result of more advanced disease at presentation. 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. In tumors thicker than 1 mm, examination of lymph nodes is generally recommended. Treatment is largely surgical.  

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.  

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.

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
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

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


