Verruciform and Condyloma-like Squamous Proliferations in the Anogenital Region

May P. Chan, MD

Context.—Histologic distinction between condyloma acuminatum and various benign and malignant condyloma-like lesions in the anogenital area poses a common diagnostic challenge to pathologists across subspecialties.

Objective.—To review the overlapping and distinguishing features of condyloma acuminatum and its mimics, and to clarify confusing terminology and diagnostic criteria for problematic entities.

Data Sources.—A review of the literature on condyloma acuminatum (ordinary and giant types), verrucous carcinoma, warty/warty-basaloid high-grade squamous intraepithelial lesion and squamous cell carcinoma, papillary squamous cell carcinoma, Bowenoid papulosis, verruca vulgaris, epidermolytic acanthoma, and verruciform xanthoma was performed.

Condyloma acuminatum frequently enters the differential diagnosis of anogenital papules or plaques, especially those with a verruciform silhouette. Classification of these lesions is often challenging owing to significant histopathologic overlap and sometimes controversial and confusing diagnostic criteria. Insufficient “crosstalk” between genitourinary, gynecologic, gastrointestinal, and general surgical pathologists and dermatopathologists further contributes to the practice gap in this area. This article reviews the clinicopathologic features and etiopathogenesis of condyloma acuminatum and its mimics, with an emphasis on their morphologic similarities and unique characteristics that help in their distinction. The clinical and pathologic features of all discussed entities are summarized in the Table.

CONDYLOMA ACUMINATUM

The incidence of condyloma acuminatum (genital wart) is highest among young adults, but has declined since the introduction of human papillomavirus (HPV) vaccines. The lesions typically arise in the genitalia, anus, and the surrounding area (pubis, groin, and medial thigh). Clinically, these are solitary or coalescent skin-colored papules with a papillomatous surface. Its giant variant (giant condyloma acuminatum of Buschke-Löwenstein) is discussed separately in the next section. Condyloma acuminatum is caused by HPV infection, with HPV types 6 and 11 being the most prevalent.5 HPV 6 and 11 belong to the low-risk HPV group, which essentially has no risk for malignant progression. Cases associated with high-grade intraepithelial neoplasia and warty/basaloid squamous cell carcinoma (SCC) are coinfected with high-risk HPV types.

The epithelium in condyloma acuminatum is acanthotic with variable degree of papillomatosis. Compared to the “spiky” papillae in verruca vulgaris (VV), the papillae in condyloma acuminatum have more rounded and undulating contours, with less robust hyperkeratosis (Figure 1, A). Collectively, these feature give rise to a “softer” appearance compared to VV. Koilocytes containing enlarged and irregular nuclei, perinuclear halos, and coarse keratohyalin granules may be found in the granular and upper spinous layers. These viral cytopathic changes serve as an important diagnostic hallmark (Figure 1, B). Binucleated or multinucleated forms may be present. The rest of the keratinocytes lack cytologic atypia and mature orderly toward the surface. A common diagnostic quandary is regarding anogenital seborrheic keratosis (SK)-like lesions without identifiable koilocytes (Figure 1, C). Multiple studies have demonstrated the presence of HPV, predominantly type 6, in up to 70% of anogenital SKs. In contrast, HPV was rarely detected in extragenital SK and other non–HPV-mediated lesions on genital skin (such as fibroepithelial polyp, epidermolytic acanthoma, and chronic dermatitis). These findings suggest that genital SK is at least similar or related to

Conclusions.—Correct diagnosis of condyloma acuminatum and condyloma-like lesions has important clinical implication and entails familiarization with their clinical presentations and histopathologic features. Contrary to historical belief, giant condyloma acuminatum and verrucous carcinoma should be considered distinct entities based on different pathogenetic pathways. Ancillary tools available for identifying and genotyping human papillomavirus can aid in diagnosis when histopathologic findings are inconclusive. Recognition of relatively rare entities such as Bowenoid papulosis, epidermolytic acanthoma, and verruciform xanthoma would avoid overdiagnosis and unnecessary, overaggressive treatment.

(Arch Pathol Lab Med. 2019;143:821–831; doi: 10.5858/arpa.2018-0039-RA)

Accepted for publication May 1, 2018.
Published online September 11, 2018.
From the Department of Pathology, University of Michigan Health System, Ann Arbor.
The author has no relevant financial interest in the products or companies described in this article.
Corresponding author: May P. Chan, MD, Department of Pathology, University of Michigan Health System, Medical Science 1 Bldg M3261, 1301 Catherine Rd, Ann Arbor, MI 48109-0602 (email: mchan@med.umich.edu).
condyloma acuminatum. Indeed, Li and Ackerman re-15 regarded HPV-harboring SK in the anogenital region as synonymous with condyloma acuminatum. As a general rule, anogenital SK-like lesions with an undulating appearance (Figure 1, C), with or without pseudohorn cysts, are probably best treated as condyloma acuminatum, as opposed to those with a flat base.15

Pirog et al 16,17 have found positive Ki-67 (MIB-1) immunostaining, defined as any cluster of at least 2 positive nuclei in the upper two-thirds of the epithelium, in all vulvar and anal condylomas examined, a finding that correlated well with positive HPV results by polymerase chain reaction (PCR) and DNA sequencing. Unlike lesions infected with high-risk HPV, which are diffusely and strongly positive for p16, condylomas display negative, focal, or patchy staining (Figure 1, D).17,18 When necessary, testing for low-risk HPV (types 6 and 11) by PCR-DNA sequencing, in situ hybridization, or immunohistochemistry may also aid in diagnosis.19

### Summary of the Clinical and Histopathologic Features of Condyloma Acuminatum and Condyloma-like Squamous Proliferations in the Anogenital Region

|                     | Condyloma Acuminatum | Giant Condyloma Acuminatum | Verrucous Carcinoma | Warty/Warty-Basaloid HSIL and SCC |
|---------------------|----------------------|---------------------------|--------------------|-------------------------------|
| **Peak age group**  | Third decade         | Third to fifth decade     | Seventh decade     | Fifth to sixth decade (HSIL); seventh decade (SCC) |
| **Common anogenital site(s)** | Any site | Penis and anorectum | Glans penis, vulva, anus | Glans penis, vulva |
| **Size**            | Small papule         | 3–13 cm                   | 1.5–5 cm           | 2–12 cm                      |
| **Configuration of papillae** | Rounded tips | Rounded tips | Broad, hypertrophic | Variable |
| **Fibrovascular cores** | Prominent | Prominent | Thin and inconspicuous | Prominent |
| **Hyperkeratosis**  | Usually mild         | Variable but usually mild | Marked, often filling spaces between verrucous projections | Usually prominent |
| **Base of tumor**   | Undulating, round    | Round, pushing            | Bulbous, pushing   | Round in intraepithelial neoplasia; infiltrative in SCC |
| **Koilocytosis**    | Present (except in SK-like lesions) | Present | Absent | Present (warty > warty-basaloid) |
| **Cytologic atypia (other than koilocytosis)** | Absent | Absent | Minimal | Prominent |
| **Mitoses**         | Few, confined to lower third of epithelium | Few, confined to lower third of epithelium | Rare, confined to basal layer | Frequent (warty-basaloid > warty), at all levels of epithelium |
| **Other characteristic findings** | N/A | N/A | Scattered dyskeratotic cells; lymphocytic band at base | Full-thickness atypia in warty-basaloid type |
| **Association with HPV** | Low-risk HPV, most commonly types 6 and 11 | Low-risk HPV, most commonly types 6 and 11 | No | High-risk HPV, most commonly type 16 |
| **Staining for p16** | Negative, focal, or patchy | Negative, focal, or patchy | Negative, focal, or patchy | Diffusely positive |

Abbreviations: HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; N/A, not applicable; SCC, squamous cell carcinoma; SK, seborrheic keratosis.

a Relevant references for condyloma acuminatum: 1, 5, 8, 9, 13, 17, 18.
b Relevant references for giant condyloma acuminatum: 20, 21, 23, 25.
c Relevant references for verrucous carcinoma: 24, 25, 28, 30, 36.
d Relevant references for warty/warty-basaloid HSIL and SCC: 39, 41, 43–47, 49.
e Relevant reference for papillary SCC: 50.
f Relevant references for Bowenoid papulosis: 52–55, 60–63.
g Relevant references for verruca vulgaris: 64–67.
h Relevant references for epidermolytic acanthoma: 68, 69, 71, 72, 82.
i Relevant references for verruciform xanthoma: 83, 84, 87, 89, 90.

### GIANT CONDYLOMA ACUMINATUM (BUSCHKE-LÖWENSTEIN TUMOR)

Giant condyloma acuminatum is a large, fungating, and locally destructive form of condyloma acuminatum. It is 3 times more common in men than women, with a predisposition for immunocompromised individuals.20 Giant condyloma acuminatum often covers multiple anatomic structures owing to its large size, most frequently involving the penis and the anorectum. The scrotum, groin, and pubis may also be affected.21–23 The tumor grows exophytically and endophytically, and the exophytic excrescences are often described as “cauliflower-like.” Fistula formation between papillae is common. Given its papillomatous architecture and large size, many regarded giant condyloma acuminatum as a variant of verrucous carcinoma. However, this view has been challenged by the frequent detection of HPV in giant condylomas but rarely in verrucous carcinomas.24,25 As in ordinary condyloma acuminatum, giant condylomas usually harbor HPV 6 and 11.24 Recurrence...
rate is high, and malignant transformation to invasive SCC has been reported in more than 50% of cases, most commonly in HIV-positive patients. Not surprisingly, coinfection with high-risk HPV has been demonstrated in carcinoma ex giant condyloma acuminatum. The microscopic features of giant condyloma acuminatum are similar to those of its ordinary counterpart except for its large size and more florid excrescences. There is marked papillomatosis with usually mild hyperkeratosis (Figure 2, A). Mitotic activity is low and is confined to the lower third of the epithelium. The large tumor mass compresses but does not infiltrate normal structures. Reverse maturation and stromal invasion, when present, should raise concern for malignant transformation. Immunohistochemical profile, including negative, focal, or patchy staining for p16, is the same as described in ordinary condyloma acuminatum.

**VERRUCOUS CARCINOMA**

Verrucous carcinoma is a unique variant of well-differentiated SCC. As mentioned above, controversy exists regarding the relationship between verrucous carcinoma and giant condyloma acuminatum. While some authors believe that the 2 are either identical or closely related on a continuous spectrum, accumulating evidence suggests that these are distinct entities. Much of the confusion stems from the lack of consistent diagnostic criteria, leading to mixed data with controversial diagnoses reported in the literature. Multiple studies have shown that unlike giant condylomas, which consistently harbor HPV, anogenital verrucous carcinomas diagnosed on the basis of strict histopathologic criteria (see below) are predominantly negative for HPV. These findings support distinct pathogenetic pathways in verrucous carcinoma and giant condyloma acuminatum, and that they should be considered separate entities. Similar to other HPV-negative SCCs of the anogenital tract, verrucous carcinoma is associated with chronic inflammatory conditions such as lichen sclerosus and lichen simplex chronicus, which play a key role in its pathogenesis.

Clinically, verrucous carcinoma and giant condyloma acuminatum share many common features including large tumor size, verrucous surface, exophytic and endophytic growth, typically slow progression, and virtual lack of metastatic potential. In addition to the anogenital area, verrucous carcinoma also occurs in the oral cavity, larynx, and extragenital skin. The warty excrescences in verrucous carcinoma tend to be coarse and irregular, whereas those in giant condyloma acuminatum are finer and more regular. Verrucous carcinoma is also more keratotic and firm than giant condyloma acuminatum, which has a more delicate and soft texture. Histopathologically, verrucous carcinoma is a well-differentiated verrucous squamous proliferation with bulbous rete ridges that push, rather than infiltrate, into the underlying stroma (Figure 3, A). Compact hyperkeratosis...
Figure 1. Condyloma acuminatum. A, A typical papillomatous papule with only mild hyperkeratosis. The papillae have mostly rounded tips and prominent fibrovascular cores. B, Koilocytes containing enlarged, irregular, and hyperchromatic nuclei, perinuclear halos, and coarse keratohyalin granules are found in the granular and upper spinous layers. The rest of the keratinocytes appear normal. C, An anogenital seborrheic keratosis with an undulating base and numerous pseudohorn cysts without evidence of koilocytosis. Similar lesions frequently harbor human papillomavirus and should at least raise suspicion for a seborrheic keratosis-like condyloma acuminatum. D, Patchy p16 immunostaining in a condyloma acuminatum (hematoxylin-eosin, original magnifications ×40 [A], ×400 [B], and ×100 [C]; original magnification ×100 [D]).

Figure 2. Giant condyloma acuminatum. A, Portion of a large, mostly exophytic, and papillomatous lesion with a “cauliflower-like” silhouette. The papillae contain prominent fibrovascular cores and lack significant hyperkeratosis, imparting a relatively “soft” appearance. The tumor base is round and noninfiltrative. B, Koilocytes are readily found in the upper epidermis, while the remaining keratinocytes are cytologically uniform and bland (hematoxylin-eosin, original magnifications ×10 [A] and ×200 [B]).
Figure 3. Verrucous carcinoma. A, An exophytic and endophytic verrucous squamous proliferation with a bulbous, pushing base. Conspicuous parakeratosis fills many gaps between the verrucous projections, giving rise to a “firm” and “rigid” appearance. Fibrovascular cores are thin and inconspicuous relative to the hypertrophic epithelium. A lymphocytic band is present at the tumor base. B, Large spinous keratinocytes contain abundant eosinophilic cytoplasm and bland nuclei. There are occasional dyskeratotic cells, while koilocytes are absent (hematoxylin-eosin, original magnifications ×10 [A] and ×400 [B]).

Figure 4. Warty and warty-basaloid high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma. A, A warty squamous cell carcinoma shows an irregular verruciform architecture with conspicuous fibrovascular cores. B, Koilocytosis and cytologic atypia are readily appreciated in this warty squamous cell carcinoma. Angulated tumor nests infiltrate the underlying stroma. C, Warty-basaloid HSIL is characterized by a verruciform architecture and basaloid epithelium with full-thickness atypia. The basaloid tumor cells display high nuclear to cytoplasmic ratio and frequent mitoses at all levels of the epithelium (inset). D, There is strong and diffuse p16 immunostaining within the lesion (hematoxylin-eosin, original magnifications ×20 [A], ×200 [B], ×40 [C], and ×200 [C, inset]; original magnification ×100 [D]).
often fills the spaces between the verrucous projections (Figure 3, A). Fibrovascular cores tend to be thin and inconspicuous relative to the hypertrophic epithelium. These features impart a “firm” and “rigid” appearance at low magnification, which contrasts with the “soft” appearance of giant condyloma acuminatum. Keratinocytes in the spinous layer are markedly enlarged with abundant eosinophilic cytoplasm and minimal nuclear atypia (Figure 3, B). Scattered dyskeratotic cells are common. An eosinophilic cytoplasm and minimal nuclear atypia (Figure 3). An important diagnostic criterion is the absence of karyolysis, which distinguishes it from giant condyloma acuminatum. Mitoses are rare and confined to the basal layer. A band of lymphocytic infiltrate is usually found at the base of the tumor (Figure 3, A).

Immunohistochemistry for p16 does not distinguish verrucous carcinoma from giant condyloma acuminatum, as both display negative or focal staining. Nuclear p53 staining is commonly present but mostly confined to the basal and suprabasal layers. Likewise, Ki-67 positivity is mainly observed in the basal layer. Absence of HPV may be confirmed by PCR-DNA sequencing, in situ hybridization, or immunohistochemistry.

**WARTY/WARTY-BASALOID HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION AND SQUAMOUS CELL CARCINOMA**

Infection by high-risk HPV, most commonly HPV 16 and less commonly HPV 18, 31, 33, 45, 51, 52, and 59 amongst others, causes undifferentiated intraepithelial neoplasia (−IN) of the vulva, vagina, penis, scrotum, and anus. These HPV-related squamous intraepithelial lesions may be classified into warty, basaloid, and warty-basaloid types by histopathologic features. To facilitate unified nomenclature across subspecialties, the Lower Anogenital Squamous Terminology (LAST) work group has recommended a 2-tier system for all HPV-associated noninvasive squamous lesions of the lower anogenital tract: low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). It is optional to further classify LSIL and HSIL as “−IN 1” and “−IN 2 or 3,” respectively, according to the specific sites. Although HSIL is synonymous with “SCC in situ” and “Bowen disease,” the latter terminologies are best avoided in pathology reporting for the purpose of consistency. Clinically, warty and warty-basaloid HSIL and invasive SCC may mimic condyloma acuminatum when discrete papillomatous papules or plaques are present.

On histopathology, warty HSIL and SCC mimic condyloma acuminatum by their verruciform architecture, conspicuous fibrovascular cores, and koilocytosis (Figure 4, A). Parakeratosis is usually more abundant than in condyloma acuminatum. The key distinguishing feature is the presence of cytologic atypia in that the keratinocytes in the lower epithelium are enlarged and pleomorphic (Figure 4, B). The upper keratinocytes acquire a moderate to abundant amount of cytoplasm as they mature toward the surface, where koilocytosis is readily appreciated (Figure 4, B). In contrast, basaloid HSIL is characterized by a flat surface and minimal maturation from the basal layer to the granular layer. While the basaloid subtype rarely mimics condyloma acuminatum, it shares overlapping features with the warty-basaloid subtype, which has a condyloma-like, verruciform silhouette (Figure 4, C). The epithelium is basaloid due to a high nuclear to cytoplasmic ratio and nuclear hyperchromasia (Figure 4, C; inset). Occasional koilocytes may be found in the upper layers. Mitoses and apoptoses are frequent and found at all levels of the epithelium (Figure 4, C; inset). When invasion occurs in the basaloid and warty-basaloid subtypes, the invasive nests often take on a basaloid appearance without keratinization. Occasionally, keratinizing SCC may occur.

As a surrogate marker for high-risk HPV infection, p16 immunohistochemical stain serves as a helpful tool to distinguish warty, basaloid, and warty-basaloid squamous neoplasms from condyloma acuminatum and HPV-independent (differentiated) squamous neoplasms. Staining in the former is strong and diffuse, and in both cytoplasmic and nuclear compartments (Figure 4, D). This is in contrast with the negative or patchy staining in condyloma acuminatum and differentiated squamous lesions. Unlike differentiated squamous lesions, p53 staining in warty, basaloid, and warty-basaloid squamous neoplasms is either negative or patchy.

**PAPILLARY SQUAMOUS CELL CARCINOMA**

HPV-independent (differentiated) squamous neoplasms seldom cause diagnostic confusion with condyloma acuminatum, with the exception of papillary SCC. The latter refers to well-differentiated SCC with a papillary architecture. This tumor type is rarely described in the anogenital region. The most comprehensive study reported 35 cases of penile papillary SCC, most of which occurred on the glans with or without involvement of the coronal sulcus and foreskin. The tumors form white-grey, irregular masses with serrated surfaces.

Microscopically, the squamous papillae are of variable lengths and shapes, lined by irregular well-differentiated squamous epithelium with overlying hyperkeratosis (Figure 5, A). Compared to condyloma acuminatum, the fibrovascular cores in papillary SCC are more irregular, and the tumor base is ragged (owing to stromal invasion) as opposed to rounded. It also differs from condyloma acuminatum and warty/warty-basaloid squamous neoplasms by the absence of koilocytes (Figure 5, B). Conspicuous fibrovascular cores and an infiltrative, rather than broad pushing, tumor base further distinguish papillary SCC from verrucous carcinoma. Differentiated intraepithelial neoplasia and lichen sclerosus may be found in the adjacent epithelium.

**BOWENOID PAPULOSIS**

Bowenoid papulosis is another HPV-associated disease affecting the squamous epithelium. Patients typically present with multiple red-brown or violaceous papules on penile or vulvar skin, although any anogenital sites may be affected. The papules have a median diameter of 0.7 cm according to one study and may be flat-topped or slightly verruciform, commonly mistaken for condyloma acuminatum on clinical examination. Most patients are young adults in the third and fourth decades of life. Similar to HSIL, Bowenoid papulosis is associated with high-risk HPV, particularly HPV 16. However, as progression to invasive SCC is exceptional, treatment options often include simple excision as well as local destructive modalities such as imiquimod and photodynamic therapy.
Figure 5. Papillary squamous cell carcinoma. A, The papillae are of variable lengths and shapes, covered by irregular well-differentiated squamous epithelium. The ragged tumor base is indicative of stromal invasion. B, Fibrovascular cores are present. There is no evidence of koilocytosis (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).

Figure 6. Bowenoid papulosis. A, This lesion shows flat acanthosis with full-thickness basoloid atypia. The tumor cells display high nuclear to cytoplasmic ratio and frequent mitoses (inset). B, The lesion is diffusely positive for p16 (hematoxylin-eosin, original magnifications ×40 [A] and ×200 [B, inset]; original magnification ×100 [B]).

Figure 7. Verruca vulgaris. A, A small verrucous papule with marked hyperkeratosis. Note the convergence of elongated rete ridges at the base. B, Many of the papillae have pointed tips surmounted by “church spire” parakeratosis. Hypergranulosis is accentuated in the “valleys” between papillae. A few koilocytes are present in the granular layer (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).
although recurrence is common.\textsuperscript{53,56–60} A small percentage of cases may regress spontaneously.\textsuperscript{53} A DNA ploidy study showed an intermediate “malignancy grade” between that of Bowen disease and SK, suggesting it to be a low-grade SCC in situ.\textsuperscript{53} Patients with bowenoid papulosis are at increased risk of developing external anogenital SCC and cervical neoplasia, and therefore warrant clinical surveillance on a regular basis.\textsuperscript{52,63}

The histopathologic features of bowenoid papulosis overlap significantly with those of basaloid HSIL (Bowen disease).\textsuperscript{52} The lesions are acanthotic and may appear psoriasiform or slightly verruciform (Figure 6, A). The keratinocytes are crowded and display high nuclear to cytoplasmic ratio and impaired maturation toward the surface (Figure 6, A; inset).\textsuperscript{54} Scattered apoptotic cells and mitotic figures are present at all levels of the epithelium.\textsuperscript{60} Some cells in the granular layer may resemble koilocytes. Pigmented lesions consist of melanophages in the underlying stroma. In a series of 108 cases, it was concluded that a background of maturing keratinocytes and sparing of the follicular epithelium could distinguish bowenoid papulosis from basaloid HSIL.\textsuperscript{53} Another morphometric analysis showed significantly larger and more irregular nuclei in basaloid HSIL compared to bowenoid papulosis.\textsuperscript{64} In practice, however, the histopathologic differences are often subtle, and definitive diagnosis relies heavily on stringent clinical correlation: Presence of multiple small pigmented papules in a young adult, as opposed to a solitary, slowly progressive plaque or erythematous patch in an older patient, would support a diagnosis of bowenoid papulosis over basaloid HSIL.\textsuperscript{53,60}

High-risk HPV in bowenoid papulosis can be detected by in situ hybridization or PCR-DNA sequencing.\textsuperscript{65–67} Expression of both p16 and human telomerase reverse transcriptase (hTERT) by immunohistochemistry is associated with high-risk HPV infection and has been demonstrated in bowenoid papulosis.\textsuperscript{67} Diffuse p16 expression is especially helpful in differentiating occasional cases of Bowenoid papulosis with more orderly maturation, subtle cytolocytic atypia, and koilocyte-like cells from condyloma acuminatum (Figure 6, B).\textsuperscript{18}

**VERRUCA VULGARIS**

Although VV (common wart) usually occurs on extragenital skin, it can occasionally arise in the anogenital area and may result in diagnostic confusion with condyloma acuminatum. Both condyloma acuminatum and VV are caused by low-risk HPV. However, in contrast with condyloma acuminatum, which is typically caused by HPV types 6 and 11, VV is most commonly induced by HPV 2, followed by HPV 1, 4, 65, 27, and others.\textsuperscript{68,69} Distinction of VV and condyloma acuminatum has important clinical implication especially in the pediatric population, as condyloma acuminatum would raise suspicion for sexual abuse, whereas VV is nonsexually transmitted. Approximately 40% of warts in the genital area of young girls are VV (positive for HPV 2) while the rest are condylomas (positive for HPV 6 or 11).\textsuperscript{70} The clinical morphologies of VV and condyloma acuminatum are similar in that both are exophytic and verrucous papules, but VV tends to be more hyperkeratotic than condyloma acuminatum.

Histopathologically, VV is characterized by marked verruiform acanthosis and hyperkeratosis. The elongated rete ridges tend to converge toward the center of the lesion (“in-toeing”) (Figure 7, A). The papillae have pointed tips and fibrovascular cores housing capillaries near the surface (Figure 7, B), which are prone to thrombosis and infarction. These papillae are surmounted by columns of parakeratosis (“church spire” parakeratosis), whereas the “valleys” between the papillae show hypergranulosis (Figure 7, B). Koilocytosis may be subtle but often can be appreciated in a background of hypergranulosis. The constellation of marked hyperkeratosis, “spiky” papillae, and convergence of elongated rete ridges allows for distinction of VV from condyloma acuminatum.

When necessary, diagnosis of VV can be confirmed by HPV genotyping. Demonstration of HPV 2 or other nongenital HPV types in the absence of HPV 6 or 11, either by in situ hybridization or by PCR-DNA sequencing, would support a diagnosis of VV and exclude condyloma acuminatum.\textsuperscript{68–72}
EPIDERMOLYTIC ACANTHOMA

Epidermolytic acanthoma can present as solitary or multiple (disseminated) lesions on the trunk, extremities, or genitalia. The disseminated form most frequently affects genital skin, particularly the scrotum and the vulva.\textsuperscript{73–75} The lesions are skin-colored or whitish papules with a smooth or verruciform surface, frequently confused with condyloma acuminatum clinically.\textsuperscript{74,76} Multiple reports have confirmed the absence of HPV in epidermolytic acanthomas,\textsuperscript{73,76,77} although 1 reported case of scrotal epidermolytic acanthoma tested positive for HPV 16 when using a highly sensitive HPV DNA chip.\textsuperscript{78} It is possible that HPV was an incidental finding, rather than a pathogenic agent, in this isolated case.

The histopathologic features of epidermolytic acanthoma frequently raise suspicion for condyloma acuminatum or VV to the untrained eye. The lesion is acanthotic and hyperkeratotic with variable degree of papillomatosis and/or invagination (Figure 8, A).\textsuperscript{76,79} The histopathologic pattern is that of epidermolytic hyperkeratosis (EHK), in which the keratinocytes in the granular and spinous layers display cytoplasmic vacuolation, reticular degeneration, coarse keratohyalin granules, and perinuclear eosinophilic inclusions (Figure 8, B).\textsuperscript{73,76,79} Despite superficial resemblance to koilocytosis, these unique characteristics of EHK effectively exclude condyloma acuminatum and VV.

Although a diagnostic hallmark of epidermolytic acanthoma, the EHK pattern is not specific for this diagnosis, as it may also be seen in epidermolytic ichthyosis,\textsuperscript{80} epidermolytic epidermal nevus,\textsuperscript{81,82} or as an incidental finding.\textsuperscript{83,84} These conditions are histologically indistinguishable, and clinical correlation is the key to correct diagnosis. Unlike epidermolytic ichthyosis, which is caused by germline mutation in KRT1 or KRT10, somatic mutations in these genes have not been found in epidermolytic acanthomas.\textsuperscript{85,86} Interestingly, however, reduced expression of cytokeratin (CK) 1 and CK10 has been demonstrated by immunohistochemistry.\textsuperscript{85,87} While the exact cause of epidermolytic acanthoma remains unclear, it has been hypothesized that repetitive trauma (scratching) or other stimuli may trigger local disruption of CK1 and CK10 protein synthesis and formation of epidermolytic acanthoma.\textsuperscript{85}

VERRUCIFORM XANTHOMA

Verruciform xanthoma is a benign proliferation most commonly occurring in the oral cavity. Extraoral lesions are rare and usually arise on the vulva, penis, scrotum, and extremities.\textsuperscript{88} Most patients present with a solitary lesion, although coexistence of multiple lesions can occur. Verruciform xanthomas are well-demarcated, yellowish-orange papules or plaques with verruciform surfaces ranging from 0.2 to 2 cm in diameter.\textsuperscript{89} Not surprisingly, the clinical morphology often raises concern for condyloma acuminatum or verrucous carcinoma.\textsuperscript{89,90} In a study of 10 vulvar verruciform xanthomas, all were associated with vulvar inflammatory or neoplastic conditions including lichen sclerosus, lichen planus, Paget disease, and radio dermatitis.\textsuperscript{89} Although HPV has been proposed in the past as the etiologic agent, multiple studies have failed to confirm a causal relationship.\textsuperscript{91–93} Based on its benign nature and association with various diseases, it is now widely believed that verruciform xanthoma represents a mucocutaneous reaction to localized trauma and chronic inflammation.\textsuperscript{84}
Histopathologic examination confirms an exophytic papillomatous lesion. A diagnostic clue at low magnification is the presence of compact parakeratosis with an orange hue or peach color completely filling the spaces between the papillary projections (Figure 9, A and B). Neutrophils are often found in the parakeratotic stratum corneum (Figure 9, B). These features should prompt a closer inspection for xanthomatous (foam) cells, which are confined to the dermal papillae (Figure 9, C). The deeper dermis is remarkable for an inflammatory infiltrate and ectatic vessels. It is hypothesized that the inciting event (trauma or other cutaneous disorder) causes keratinocytic degeneration and release of cellular lipids and chemokines, which then lead to a foam cell response, chemotaxis of neutrophils, and stimulation of epidermal proliferation.

The absence of cytolytic atypia and koilocytosis in verruciform xanthoma speaks against condyloma acuminatum, and the presence of xanthomatous cells excludes verrucous carcinoma.

CONCLUSIONS

Besides condyloma acuminatum, a number of cutaneous and mucosal lesions in the anogenital region share a similar verruciform architecture and/or clinical presentation, often representing a common source of diagnostic confusion. Amongst these are relatively rare entities such as Bowenoid papulosis, epidermolytic acanthoma, and verruciform xanthoma, which are unrecognized by surgical pathologists. Giant condyoma acuminatum and verrucous carcinoma used to be considered synonymous, but accumulating evidence supports that these are distinct entities with different pathogenetic pathways. Familiarization with the clinicopathologic characteristics and HPV status of various anogenital lesions described in this review should allow for more accurate classification and appropriate management of these conditions.

References
1. Patel H, Wagner M, Singhal P, Kohli S. Systematic review of the incidence and prevalence of genital warts. BMC Infect Dis. 2013;13:39.
2. Bauer HM, Wright G, Chow J. Evidence of human papillomavirus vaccine effectiveness in reducing genital warts: an analysis of California public family planning administrative claims data, 2007-2010. Am J Public Health. 2012;102(9):833–835.
3. Guerra FM, Rosella LC, Dunn S, Wilson SE, Chen C, Deeks SL. Early impact of Ontario’s human papillomavirus (HPV) vaccination program on anogenital warts (AGWIs): a population-based assessment. Vaccine. 2016;34(39):4678–4683.
4. Canvin M, Sinha K, Hughes G, Mesher D. Decline in genital warts diagnoses among young women and young men since the introduction of the bivalent HPV 16/18 vaccination programme in England: an ecological analysis. Sex Transm Infect. 2017;93(2):125–128.
5. Cong X, Sun R, Zhang X, Wang Y, Wang L, Yu Y. Correlation of human papillomavirus types with clinical features of patients with condyloma acuminatum. Arch Dermatol. 2016;155(7):775–780.
6. Maniar KP, Ronnett BM, Yemelyanova A. Coexisting high-grade vulvar intraepithelial neoplasia (VIN) and condyloma acuminatum: independent relationships due to different HPV types occurring in immunocompromised patients. Am J Surg Pathol. 2013;37(1):53–60.
7. Erman-Vlahovic M, Vlahovic M, Mrclsa M, Hrgovic Z. Coexistence of condylomata acuminata with warty squamous cell carcinoma and squamous cell carcinoma. Med Arch. 2017;71(1):72–75.
8. Fernández-Nestos MJ, Guimerá N, Sanchez DF, et al. Human papillomavirus (HPV) genotypes in condylomas, intraepithelial neoplasia, and invasive carcinoma of the penis using laser capture microdissection (LCM-PCR): a study of 191 lesions in 43 patients. Am J Surg Pathol. 2017;41(6):820–832.
9. Nuovo GJ, O’Connell M, Blanco JS, Levine RJ, Silverstein SJ. Correlation of histology and human papillomavirus DNA detection in condyloma acuminatum and condyloma-like vulvar lesions. Am J Surg Pathol. 1989;13(8):700–706.
10. Leonardi CL, Zhu WY, Kinsey WH, Penneys NS. Seborrhoeic keratoses from the genital region may contain human papillomavirus DNA. Arch Dermatol. 1991;127(8):1203–1206.
11. Zhu WY, Leonardi C, Penneys NS. Detection of human papillomavirus DNA in seborrhoeic keratosis by polymerase chain reaction. J Dermatol Sci. 1992;4(3):166–171.
12. Bai H, Ciko A, Granter S, Yuan L, Betensky RA, Crum CP. Immunohistochemical pattern of human papillomavirus correlates of vulvar seborrheic keratosis. J Cutan Pathol. 2013;40(2):94–99.
13. Tardito JC, Bancalari E, Moreno A, Martin-Fragueiro LM. Genital seborrhoeic keratoses are human papillomavirus-related lesions: a linear array genotyping test study. APMIS. 2012;120(6):477–483.
14. Reutter JC, Geisinger KR, Lauadio J. Vulvar seborrhoeic keratosis: is there a relationship to human papillomavirus? J Low Genit Tract Dis. 2014;18(2):190–194.
15. Li J, Ackerman AB. “Seborrhoeic keratoses” that contain human papillomavirus are condylomata acuminata. Am J Dermatopath. 1994;16(4):398–403.
16. Canvin M, Sinka K, Hughes G, Mesher D. Decline in genital warts due to different HPV types occurring in immunocompromised patients. J Gen Intern Med. 2013;28(6):920–924.
17. Trombetta LJ, Place RJ. Giant condyoma acuminatum of the anorectum: trends in epidemiology and management: report of a case and review of the literature. Dis Col Rectum. 2001;44(12):1878–1886.
18. Zhu WY, Velezgaitas MP, Libby NP, Wang YJ, Hjalmarson R. Giant condyoma acuminatum (Buschke-Loewenstein tumor) of the anorectal and perianal regions: analysis of 42 cases. Dis Colon Rectum. 1994;37(9):950–957.
19. Nain PS, Sidhu S, Garg B. Giant condyoma acuminatum of the inguinal region. Indian J Surg. 2015;77(suppl 2):729–730.
20. Ogrodnik J, Galati S, Hodgett J, Koomce M. Giant condyoma acuminatum of the anogenital region. Int J Gynaecol Cancer. 2010;20(10):1449–1455.
21. Kozlouskaya V, Shustef E, Allam SH, Lal K, Elston D. Expression of p16 protein in lesional and perilesional condyloma acuminata and bowenoid papulosis: clinical significance and diagnostic implications. J Acad Dermatol. 2013;69(4):444–449.
22. Witasickuannukul J, Klump VR Jr, McNiff JM, Ko CJ. Detecting HPV in cutaneous lesions using anti-HPV antibody immunohistochemistry. Am J Dermatopath. 2013;35(1):32–38.
23. del Pino M, Bleeker MC, Quint WG, Sniijders PJ, Meijer CJ, Steenbergen RD. Comprehensive analysis of human papillomavirus prevalence and the potential role of low-risk types in verrucous carcinoma. Mod Pathol. 2012;25(10):1334–1363.
24. Zidar N, Langner C, Odar K, et al. Analog verrucous carcinoma is not related to infection with human papillomaviruses and should be distinguished from giant condyloma (Buschke-Loewenstein tumour). Histopathology. 2017;70(6):938–945.
25. Diani M, Boneschi V, Ramoni S, Gaffa D, Del Gobbo A, Cusini M. Rapidly invasive Buschke-Loewenstein tumour associated with human papillomavirus types 6 and 32. Sex Transm Dis. 2015;42(10):547–548.
26. Banthao C, Nokes-Moore S, Shier M. Giant condyoma acuminatum versus verrucous carcinoma: a case report. J Low Genit Tract Dis. 2010;14(3):230–233.
27. Gualco M, Bonin S, Foglia G, et al. Morphologic and biologic studies on ten cases of verrucous carcinoma of the vulva supporting the theory of a discrete clinico-pathologic entity. J Gynecol Cancer. 2003;13(1):317–324.
28. Capoccetta AF, Granter SR, Ciko A, Yuan J, Hecht JL, Crum CP. Vulvar acanthosis with altered differentiation: a precursor to verrucous carcinoma? Am J Surg Pathol. 2004;28(5):638–643.
29. Stankewicz E, Kudahetti SC, Prowse DM, et al. HPV infection and immunohistochemical detection of cell-cycle markers in verrucous carcinoma of the penis. Mod Pathol. 2009;22(9):1160–1168.
30. Klima M, Kurtis B, Jordan PH Jr. Verrucous carcinoma of skin. J Cutan Pathol. 1980;7(2):88–98.
31. Bain L, Geronomus R. The association of lichen planus of the penis with giant condyloma acuminatum. Histopathology. 1980;7(2):88–98.
32. Bain L, Geronomus R. The association of lichen planus of the penis with giant condyloma acuminatum. Histopathology. 1980;7(2):88–98.
33. Klima M, Kurtis B, Jordan PH Jr. Verrucous carcinoma of skin. J Cutan Pathol. 1980;7(2):88–98.
34. Klima M, Kurtis B, Jordan PH Jr. Verrucous carcinoma of skin. J Cutan Pathol. 1980;7(2):88–98.
35. Klima M, Kurtis B, Jordan PH Jr. Verrucous carcinoma of skin. J Cutan Pathol. 1980;7(2):88–98.
51 in Bowenoid papulosis demonstrated by DNA in situ hybridization.

J Dermatol

virus DNA in bowenoid papulosis, Bowen’s disease and squamous cell

Br J Dermatol

DNA in a patient with Bowenoid papulosis that progressed to squamous cell

J Am Acad

therapy for bowenoid papulosis using a novel incoherent light-emitting diode
device.

113.

device.

107–112.

113:10:1266–1297.

distribution and characterization of subtypes of penile intraepithelial neoplasia and their association with invasive
carcinomas: a pathological study of 139 lesions in 121 patients. 

Hum Pathol.

2012;43(7):1020–1027.

51. Chaux A, Planell R, Rodrigue IM, et al. Distinctive immunohistochemical

profile of penile intraepithelial lesions: a study of 74 cases. 

J Am Acad Dermatol

2010;63(4):553–561.

107–112.

107–112.

113:11:115–1356.

107–112.

113:11:115–1356.

107–112.

113:11:115–1356.

107–112.

113:11:115–1356.

107–112.

113:11:115–1356.

vulvar squamous cell carcinomas.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.

83–136.