Cutaneous manifestations of human papillomaviruses: A review

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KEY WORDS

human papillomavirus, common warts, plantar warts, plane warts, condyloma acuminatum, Bowenoid papulosis, epidermodysplasia verruciformis

ABSTRACT

Human papillomaviruses (HPVs) are small DNA viruses of the papovavirus family, with more than 100 types already described. Their importance in human disease cannot be overemphasized because these agents are among the most common pathogens in cutaneous infectious diseases and are very important in a subset of predominantly, but not exclusively, genital squamous-cell carcinomas. HPVs can be associated with a variety of cutaneous as well as mucosal manifestations. Some types of HPVs are associated with increased risk of epithelial malignancies; these have been divided into low-risk and high-risk types based on their oncogenic potential. Clinical and histological features of HPV infection vary according to individual susceptibility (e.g., immunosuppressed patients), site of involvement, and type of HPV implicated. The histological features of HPV infection are very easy to identify on sections stained with hematoxylin and eosin. However, many findings usually associated with HPV infection are entirely non-specific. Additional current diagnostic methods for identification of HPV in tissues include techniques based on the detection of viral DNA; namely, in-situ hybridization and polymerase chain reaction (PCR). This article reviews the main clinical and histopathological cutaneous manifestations of HPV infection, including common warts, plantar warts, plane warts, condyloma acuminatum, Bowenoid papulosis, and epidermodysplasia verruciformis. Emphasis is placed on the clinical and histological features of these various manifestations, including a brief discussion about the routinely used laboratory methods for detecting HPV in tissues.

Introduction

Human papillomaviruses (HPVs) are small DNA viruses of the papovavirus family. Currently over 100 different types of HPVs have been described (1). Genotypes are defined according to the DNA homology in certain sequences of the viral genome: a new type is defined when a given HPV shows more than 10% divergence in the L1 sequence when compared with any of the known HPV types by DNA hybridization (2). In contrast, subtypes differ by 2 to 10% in their DNA sequence from any virus within a known type, and variants differ by only 2% or less (3).

HPVs are non-enveloped, very resistant viruses with a diameter of 55 nm (4). Their genome consists of a circular DNA double strand containing approximately 8,000 nucleotide base pairs, associated with histones forming a structure that has been compared to a "minichromosome" (4). The viral genome is enclosed in an icosahedral capsid composed of 72 capsomers (1, 5). The genome encodes for seven to nine open reading frames (ORFs) depending on the genotype, and can be divided into a coding region and a non-coding region called the long control region (LCR) or upstream regulatory region (URR). The coding region encodes early (E) and late (L) proteins. The LCR/URR is important in regulating the expression of all HPV genes because it contains promoters and transcriptional enhancer sequences (1, 2, 4). Early proteins are involved in transcription, replication, and cellular transformation, and include the proteins E1, E2, E4, E5, E6, and E7 (1). Some of these proteins interfere directly with the structure and function of keratinocytes. For example, some forms of E4 protein disrupt the cytokeratin network, leading to the phenomenon of koilocytosis (1, 2). E6 and E7 interfere with the cell cycle and apoptosis mechanisms, potentially leading to proliferation and transformation, which appears to be an important mechanism in the process of carcinogenesis induced by certain types of HPV (4). L1 and L2 genes encode the proteins of the viral capsid (2).

For practical and clinical purposes, HPVs can be classified as mucosal and cutaneous types according to their tropism. The cutaneous types can be classified as those common to the general population (e.g., HPVs 1, 2, and 4) and those associated with epidermodysplasia verruciformis (EV) (2). The latter group includes numerous types, of which HPV-5 and -8 are particularly important due to their higher risk of inducing malignant transformation (1, 2, 4). The mucosal types are generally subdivided into high-risk and low-risk types. Low-risk types are defined by the fact that they are almost never found in invasive squamous-cell carcinomas, and the most relevant types are HPV-6 and -11. High-risk types include HPV-16 and -18, and a category of moderate- to high-risk types includes HPV-31, -33, -35, -52, -58, and -67 (2).

Transmission of HPV requires inoculation of the virus into the cells of the basal epithelial layer, which is thought to occur in sites prone to microinjuries (4). It is therefore not surprising that common warts, for example, occur more frequently on the hands and fingers. Detection of HPV by in-situ hybridization studies have shown, however, that the most active viral replication occurs in the superficial spinous layer, and that assembly of the viral particle occurs in the granular cell layer (1, 6). However, it has been demonstrated that the virus also maintains a low level of replicative activity in the basal cell layer, thus ensuring its persistence in the tissues (4). Regression of HPV lesions is frequently spontaneous, and immune mechanisms are believed to play an important role in this phenomenon. However, resolution is frequently slow (up to several years), probably because immune mechanisms are less effective against infected cells located superficially due to the absence of direct blood supply (1). The immune mechanisms in the response against HPV seem to be at least partially dependent on cell-mediated immunity because lymphocytes are seen infiltrating regressing warts, sometimes in the context of a lichenoid tissue reaction. The innate immune response, namely the recognition of viral particles by the Toll-like receptors (TLR)-3 and -9, as well as the secretion of interferon (IFN)-β and TNF-α, also appear to be an important part of the immune response against HPV (7). In addition to lymphocytes, Langerhans cells and Langerhans-like dendritic cells may also play a role in the immune response against HPV (1). The important role of the immune system against HPV is easily inferred from the greater susceptibility of immunosuppressed patients to HPV disease, which is then frequently more exuberant and more resistant to treatment.

The mechanism of malignant transformation induced by high-risk HPV types is not completely understood. Integration of the virus seems to be an important event in malignant transformation induced by high-risk genital HPV-types. Interestingly, however, this phenomenon does not seem to be necessary for the carcinogenesis induced by EV-related HPVs (4). The best-documented mechanism in HPV-related malignant transformation is the persistent overexpression of the proteins E6 and E7. E6 interferes with the function of p53 and E7 with the function of Rb protein. Acting synergistically, they promote inhibition of apoptosis and dysregulation of the cell cycle, respectively, leading to abnormal cell growth (4).

HPV cannot be grown in conventional cell cultures. Furthermore, the fact that it induces a humoral response that remains detectable for many years makes serology an unreliable method to distinguish between present and past infections. Consequently, demonstration of the presence of HPV in the tissues depends on the identification of viral nucleic acids. In-situ hybridization is based on the use of labeled probes that specifically bind sequences of viral DNA. In order to identify the different genotypes, probes with specific sequences for each genotype are required. There are commercially available kits that include cocktails of probes directed to detect the most common high and low-risk types of HPV in the tissue. These techniques can be used in formalin-fixed paraffin-embedded tissue. It is important to stress, however, that these

cocktails do not contain less common genotypes (including, for example, the types implicated in epidermodysplasia verruciformis), and so false negative reactions may occur.

DNA amplification techniques (polymerase chain reaction [PCR] and its variants) can be used to detect HPV in a given tissue, either by using a broad-spectrum method (which uses a highly conserved DNA sequence among all HPV types as a target) or, alternatively, using type-specific sequences in order to determine the exact genotype implicated. The latter method is not usually used routinely but is of importance in specific settings (8).

HPVs are associated with a variety of cutaneous manifestations, including common warts (verrucae vulgaris), plantar warts, plane warts (verrucae plana), anogenital warts, and epidermodysplasia verruciformis. Mucosal manifestations include oral warts and condylomata, focal epithelial hyperplasia (Heck's disease), nasal and conjuntival papillomas, laryngeal papillomatosis, and cervical lesions. The role of oncogenic types of HPV has been recognized for many years in the genesis of cervical cancer and it is also increasingly being demonstrated in a variety of other neoplasms, such as cancers of the anal and external genital areas (1). A review of the most important manifestations of cutaneous HPVs follows.

Common warts

Common warts (verrucae vulgaris) are usually caused by HPV types 1, 2, and 4. HPV-7 is associated with the "butcher's warts." Occasionally other genotypes have been associated, particularly in immunosuppressed patients (e.g., HPV-75–77) (1). There is a high incidence in the general population, particularly in children. Estimated frequencies point to a prevalence of 3.5% in adults (9) and up to 33% in primary schoolchildren (10). There is an increased incidence in immunosuppressed patients, including in HIV and transplant patients, and these patients are susceptible to having more numerous and more recalcitrant lesions. Lesions may regress after restoration of the immune system; for example, after highly active antiretroviral therapy (HAART) for HIV (11).

Involvement is more frequently seen on the hands, particularly the fingers, and lesions present as small (usually 1 to 10 mm, rarely more) dome-shaped papules with a keratotic and verrucous surface. Lesions may also appear in other locations, such as the elbows, knees, and face. In the latter location, especially in periorificial areas, the lesions are frequently filiform in appearance (1).

Histologically, the lesions are characterized by hyperkeratosis, papillomatosis, and acanthosis. These features are non-specific and are seen in many cutaneous lesions not associated with HPV infections. Architecturally there is frequently an inward projection of the adjacent elongated rete ridges, giving a curvilinear appearance to the base of the lesion. In the stratum corneum there are frequently tiers of parakeratosis overlying the tips of the papillomatous projections, alternating with orthokeratosis overlying the concavities (Figure 1). The granular layer is often increased, and the keratohyaline granules appear coarse and clumped (Figure 2). Cells with a picnotic nucleus surrounded by a clear halo (koilocytes), which are the hallmark of the cytopathogenic effect of HPV, are characteristic but not always found, being more frequent in genital lesions. Additional features may include the presence of tortuous blood vessels in the dermal papillae (1). The presence of the virus can be

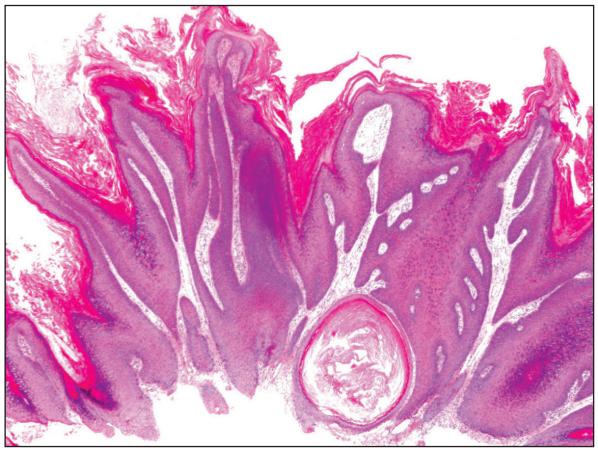

Figure 1. Common wart. Prominent acanthosis, papillomatosis, and hyperkeratosis. Note inward projection of the elongated rete ridges.

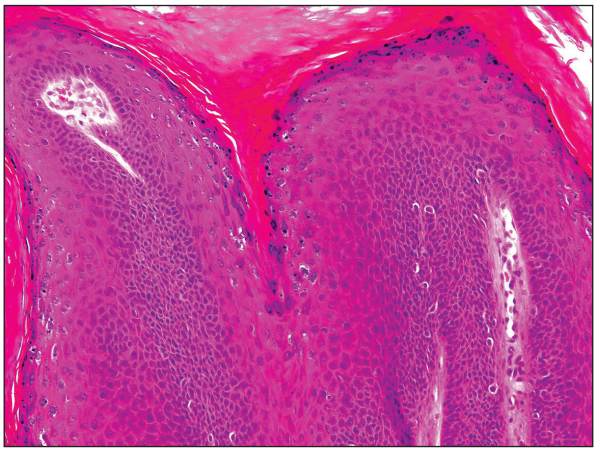

Figure 2. Common wart. Coarse and clumped keratohyalin granules.

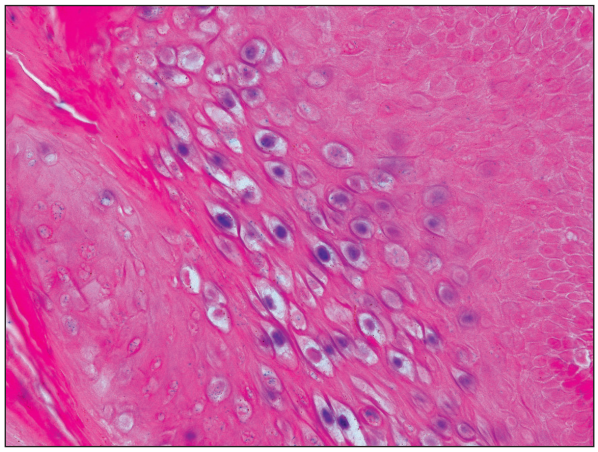

Figure 3. In-situ hybridization for low-risk HPV in a common wart showing prominent nuclear positivity.

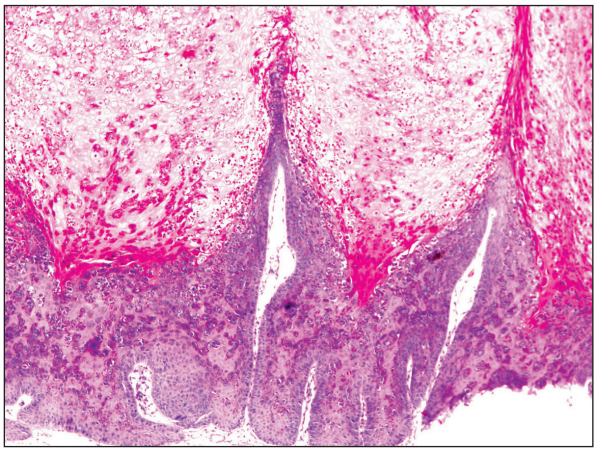

Figure 4. Plantar wart. Similar histological features to those of a common wart but with endophytic growth and prominent clumps of eosinophilic material are seen in the stratum corneum and within the cytoplasm of keratinocytes

demonstrated by in-situ hybridization in paraffin sections (Figure 3). In some cases, the involvement of the epithelium of hair follicles may result in changes reminiscent of trichilemmoma or inverted follicular keratosis, which led some researchers in the past to conclude that the latter lesions were induced by HPV infection (12). However, a recent study has failed to demonstrate the presence of HPV DNA in a group of trichilemmomas tested (13).

Squamous-cell carcinoma arising in common warts is a very rare phenomenon (1) and has been described including in the setting of immunosuppression (14). A synergistic role of sun exposure as a co-carcinogenic factor with the virus has been hypothesized in this setting (14).

Plantar warts

Plantar warts occur on the sole of the foot and are more common in children. They are more commonly associated with HPV-1 and sometimes HPV-4. Other rarer types include HPV types 57, 60, 63, 65, and 66 (1). HPV-57 and -60 have also been associated with epidermoid cysts occurring on the sole of the foot in Japanese patients (15, 16).

Clinically, HPV-1 more commonly induces lesions that present as a keratotic plug surrounded by a hyperkeratotic rim, usually only slightly elevated, and frequently painful. Lesions frequently contain multiple black dots scattered over the surface, which represent thrombosed capillaries, and are a very useful clinical diagnostic clue. They occur commonly at pressure points. HPV-4 is associated with mosaic warts, which are more superficial lesions that occur in a confluent cobblestone pattern and are usually painless (1).

The lesions tend to be self-resolving, although complete resolution may take years. Its natural course tends to be shorter in children than in adults (1).

Histologically, plantar warts are characterized by acanthosis and papillomatosis, and typically have an endophytic growth (Figure 4). The downward extension of the intercommunicating rete ridges has been compared to an anthill; hence the designation "myrmecia." The cells in the granular layer, apart from the vacuolation common to other viral warts, also frequently show very characteristic brightly eosinophilic cytoplasmic inclusions, which represent altered keratohyaline granules (Figure 5). Lesions with these

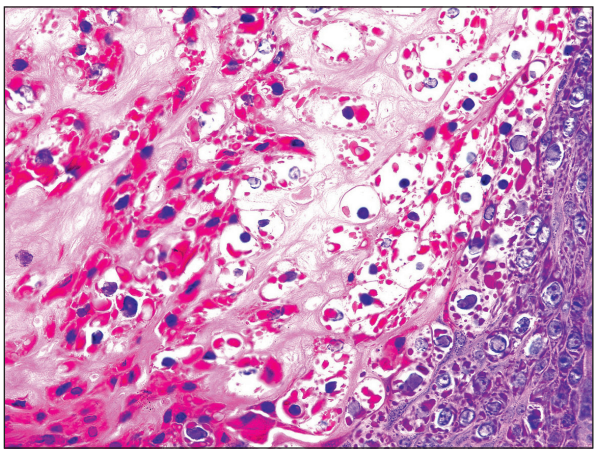

Figure 5. Plantar wart. Bright eosinophilic cytoplasmic inclusions.

features are frequently caused by HPV-1. In contrast, lesions induced by HPV-4 tend show mainly vacuolation without prominent keratohyaline granules. Some lesions induced by HPV-60 may be pigmented, containing melanin granules in the cytoplasm of keratinocytes (1).

Only very rarely may longstanding plantar lesions be associated with the development of verrucous carcinoma (carcinoma cuniculatum) (17).

Plane warts

Plane warts are very common, especially in children. Occasionally, they may be seen in adult women, but they are rare in men except in the context of HIV infection. They are more commonly caused by HPV types 3 and 10, and occasionally types 26–29 and 41 (1). HPV-5 (an EV-related HPV type) has been described in the setting of HIV infection (18).

Clinically, lesions most commonly involve the face, the dorsum of the hands, and the shins (1). They are usually multiple and consist of flat-topped smooth-surfaced papules, usually with a light brown color that may be so light as to simulate the color of normal skin. This feature sometimes leads to underestimation of their extent. Koebnerization is a well-described phenomenon in plane warts (1). Lesions may regress spontaneously, and this may be accompanied by pruritus, inflammation surrounding the area, or depigmented halos (19). Regression may be preceded by an eruption of multiple warts (20). Interestingly, an eruption of plane warts has been described as a sign of the immune reconstitution inflammatory syndrome (IRIS) in HIV-positive patients (21).

Histologically, plane warts are characterized by acanthosis and typically prominent koilocytic change in the granular cell layer. In contrast to common and plantar warts, papillomatosis is only mild or absent and the stratum corneum is characterized by basket-weave orthokeratosis with no parakeratosis (Figures 6 and 7). Regressing lesions are characterized by apoptosis of keratinocytes, spongiosis, exocytosis of lymphocytes, and underlying chronic perivascular inflammation (1).

Condyloma acuminatum

Condyloma acuminatum usually manifests as multiple exophytic papillomatous lesions that more commonly affect the anogenital area (1). In men, genital condylomas more commonly involve the coronal sulcus, the glans penis, and the penile shaft, and they are more frequent in uncircumcised men (22). In women, lesions commonly affect the external genitalia, such as the vulvar vestibulum (1), but lesions can also be found in the cervix (23). Immunosuppressed patients may have more prominent lesions (24), which are frequently more resistant to treatment. Recurrences are frequent and occur in up to one-third of cases (25).

Condylomas are usually sexually transmitted and are more frequently caused by HPV types 6 and 11, although many other genotypes have also been described, including 2, 16, 18, 30–33, 35, 39, 41–45, 51–56, and 59 (1), many of which are intermediate- and high-risk types. More than one type may be implicated in a single case (26).

The presence of warty lesions in the anogenital area in children raises the suspicion of sexual abuse. However, it is important to stress out that warty lesions in the anogenital area in children are frequently caused by non-genital HPV types and therefore many of these cases may not be of sexual transmission (27,

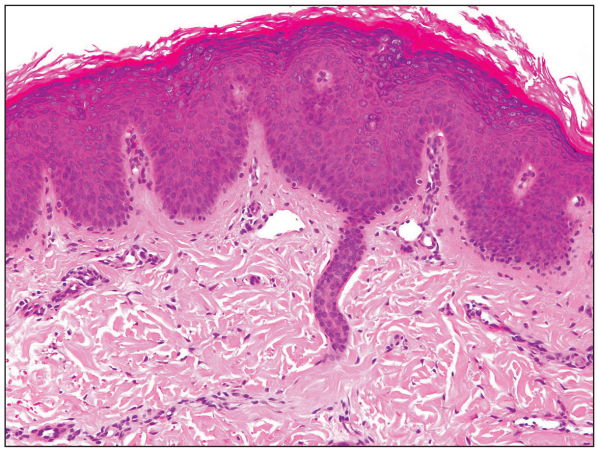

Figure 6. Plane wart. Acanthosis is milder than in other types of viral warts and papillomatosis is absent or minimal.

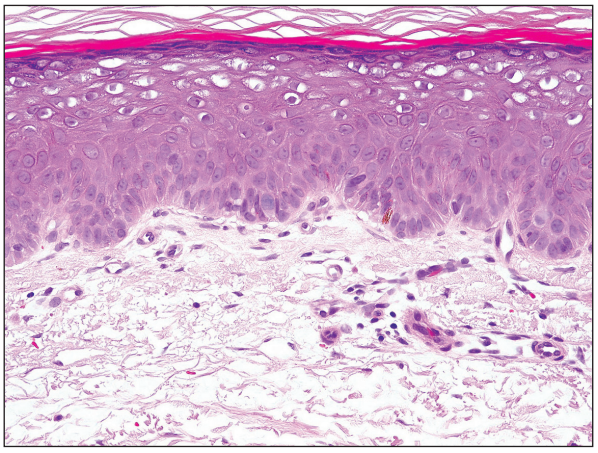

Figure 7. Plane wart. Keratinocytes in the upper layers of the epidermis appear vacuolated but koilocytes are not usually seen.

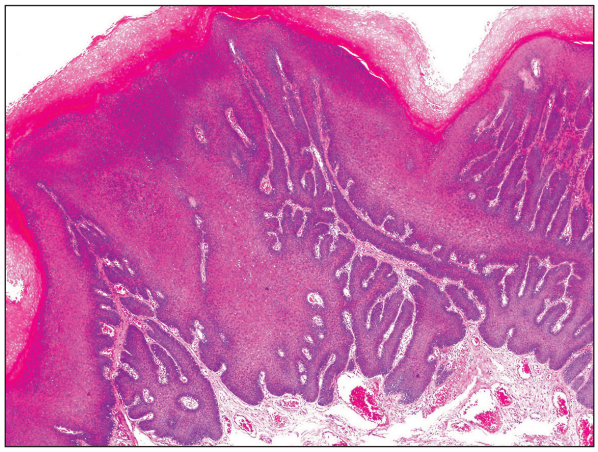

Figure 8. Condyloma acuminatum. Prominent acanthosis, hypergranulosis, hyperkeratosis, and elongated bulbous rete ridges.

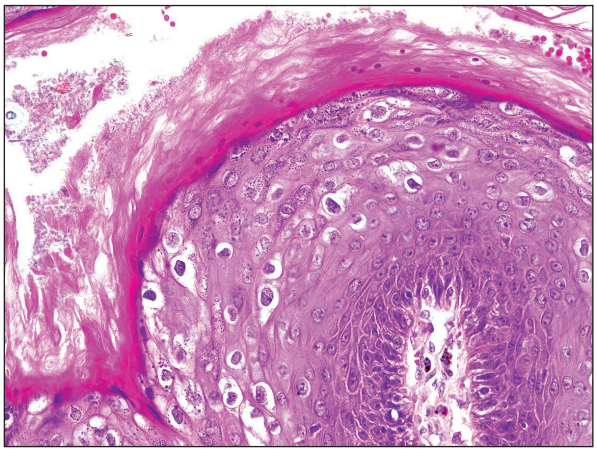

Figure 9. Condyloma acuminatum. Koilocytes (keratinocytes with picnotic and hyperchromatic nuclei) are frequent and there is also clumping of keratohyalin granules.

28). Condylomata in children regress in up to 50% of cases (29).

Giant condyloma acuminatum of Buschke-Lowenstein is clinically characterized by a large exophytic tumor with a verrucous surface (frequently referred to as a cauliflower-like appearance) (30), which may be ulcerated, and more commonly involves the penis or the perianal area. It is nowadays regarded by most authors as a variant of verrucous carcinoma, although this view is not undisputed (30, 31). It is usually caused by HPV types 6, 11, and 16 (1).

Histologically, condyloma acuminatum is an exophytic lesion characterized by hyperkeratosis with parakeratosis, papillomatosis, and marked acanthosis (Figure 8). Koilocytes in the granular layer, as well as coarse keratohyaline granules are characteristic features (1) (Figure 9). Lesions resembling seborrheic keratoses can be seen (32). Treatment with podophyllin (which is seldom used now since the introduction of imiquimod) may result in atypical histological features, including increased mitotic activity (33).

Giant condyloma acuminatum of Buschke-Lowenstein is usually a large exo-endophytic tumor with a hyperkeratotic surface and few or no koilocytic changes in the granular cell layer. Cytologically the lesion consists of cells with little or no atypia, which typically have abundant pale pink cytoplasm and exhibit good maturation towards the surface. Large bulbous rete ridges with a pushing border that frequently involves deep structures like the corpora cavernosa characterize the deeper part of the tumor. These features found in the deep portion of the lesion are particularly important for the diagnosis, and so this finding is usually not possible in superficial biopsy specimens (30).

Bowenoid papulosis/ undifferentiated intraepithelial neoplasia

Bowenoid papulosis is the term used to describe the presence of usually multiple papules, which may be lichenoid in appearance and are characterized histologically by Bowenoid (full-thickness) dysplasia (1, 3, 4). Lesions more frequently involve the anogenital area (e.g., penis, foreskin, and perianal area), but they have been described occasionally in other locations (1). Lesions are frequently pigmented (34) and occasionally they may be confluent. Although the term "Bowenoid papulosis" is not officially recognized anymore, it is still used by many clinicians because the clinicopathological features of this entity are fairly distinctive (1). It is currently recommended that this should only be regarded as a form of intraepithelial dysplasia/squamous-cell carcinoma in situ, instead of distinguishing it from other entities based only on the different clinical presentation.

In the vulva, for example, all forms of epithelial dysplasia are currently referred to as vulvar intraepithelial neoplasia (VIN), irrespective of their clinical presentation. It used to be classified into VIN 1, 2, and 3 (similarly to cervical intraepithelial neoplasia [CIN]) but is now divided into differentiated and undifferentiated forms. Differentiated types are usually not associated with HPV infection, but with other conditions such as lichen sclerosus. Undifferentiated VIN is usually associated with HPV infection, and is further subdivided into warty and basaloid types, based on the histological features (35).

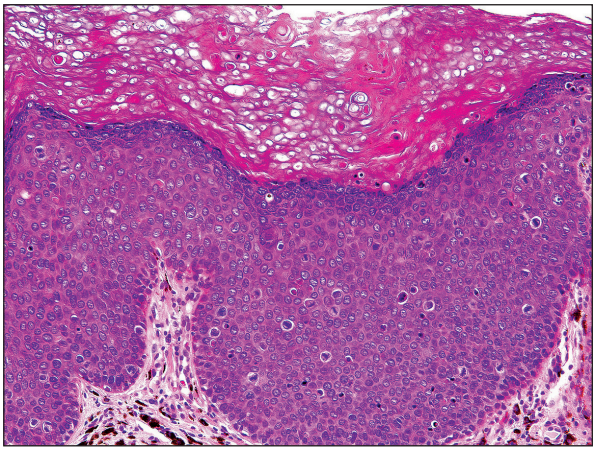

Figure 10. Undifferentiated intraepithelial neoplasia. Full thickness epidermal dysplasia with basaloid atypical cells and frequent mitotic figures.

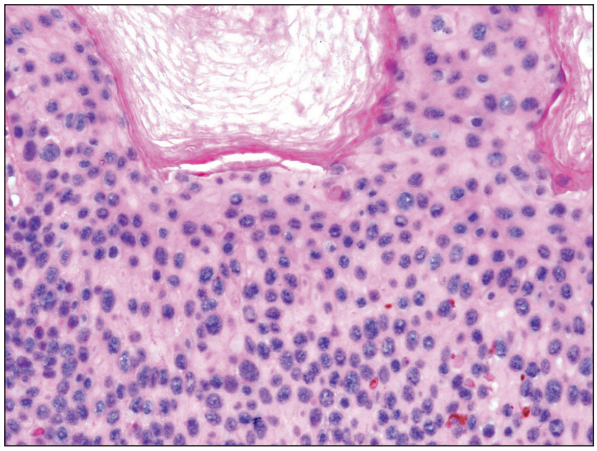

Figure 11. Undifferentiated intraepithelial neoplasia. In-situ hybridization for high-risk HPV shows prominent nuclear positivity in most cells.

Histologically, Bowenoid papulosis/undifferentiated intraepithelial neoplasia is characterized by a well-demarcated area of acanthosis, with full-thickness cytological atypia, which may be indistinguishable from other forms of squamous-cell carcinoma in situ. However, some histological peculiarities may point to this diagnosis, and these include a high number of mitotic figures, numerous dyskeratotic cells, and the presence of partly vacuolated cells. The final diagnosis rests on clinicopathological correlation (1).

VIN is characterized by full-thickness keratinocytic dysplasia (Figures 10 and 11). The warty type is characterized by marked pleomorphism with abnormal mitoses and individual cell keratinization. Basaloid VIN, as the name implies, is characterized by full-thickness dysplasia composed predominantly of cells resembling the basal keratinocytes, with a hyperchromatic nucleus and scanty cytoplasm accounting for its histological appearance (35).

Epidermodysplasia verruciformis

In its classic form, epidermodysplasia verruciformis (EV) is a rare genodermatosis with an autosomal recessive mode of inheritance. It is currently considered a form of primary immunodeficiency characterized by susceptibility for infection with β-HPV subtypes (4). Interestingly, it is not associated with susceptibility to infections caused by other pathogens. Most cases (approximately 75%) are caused by homozygous frameshift, nonsense, or splice-site mutations in one of two genes located in the long arm of chromosome 17 (EVER1 or TMC6, and EVER2 or TMC8) (36). These genes encode for transmembrane proteins that are predominantly expressed in the endoplasmic reticulum and interact with a zinc transporter (ZT1), contributing to the maintenance of intracellular zinc homeostasis. Disruption of this homeostasis is believed to lead to susceptibility to infection by β-HPV subtypes (4). The most frequently implicated types are HPV-5 and -8, but numerous others have been described, including 3, 9, 10, 12, 14, 15, 17, 19–25, 28, 29, 36–38, 46, 47, 49–51, and 59 (1, 4, 36–38).

Clinically, epidermodysplasia verruciformis is characterized by the early onset of multiple flat warts, pityriasis versicolor-like lesions, and lesions resembling seborrheic keratoses (1) (Figure 12). Patients have an increased risk (in about 30 to 50% of cases, or even more) of squamous-cell carcinomas, which more frequently arise in sun-exposed skin (1, 4). Development of malignant transformation is usually associated with HPV types 5 and 8. However, the mechanism of carcinogenesis induced by EV-related HPV types is not clear; in contrast to the other oncogenic HPVs, these do not seem to need integration into the host's genome (4).

More recently, an EV-like clinical picture has been described in immunosuppressed patients; namely, in the setting of HIV infection (including congenital infection) and in transplant recipient patients (37, 38). This form has been named "acquired epidermodysplasia verruciformis" (37). Some authors have hypothesized that these patients may in fact have milder genetic defects in genes predisposing to EV that are then made clinically apparent by the superimposed immunosuppression (36). Lesions tend to be very difficult or even impossible to treat, even after the introduction of HAART for HIV (38). Many children born with HIV infection in Africa present with an epidermodysplasia verruciformis-like picture that is

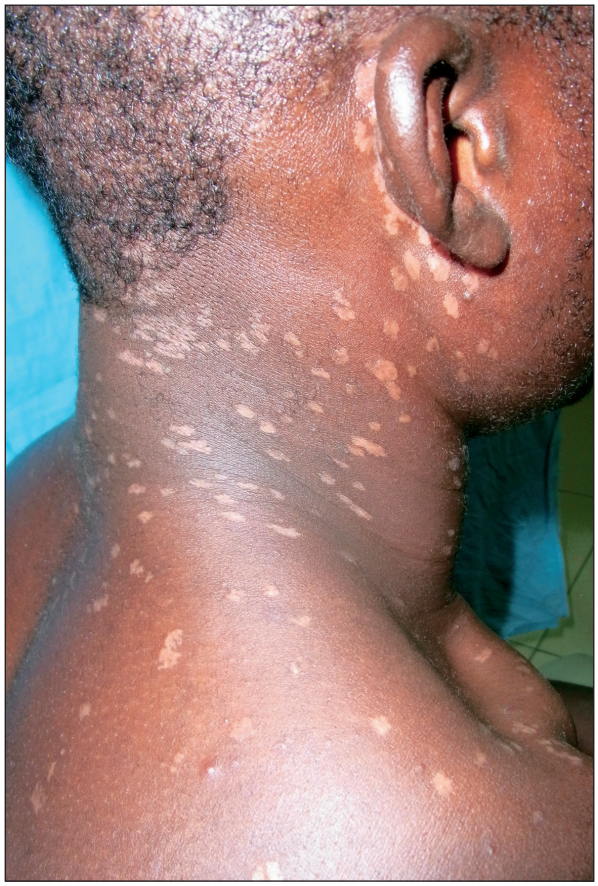

Figure 12. Epidermodysplasia verruciformis. Affected patients often present with numerous scaly hypopigmented lesions (courtesy of F. Ajose, Lagos, Nigeria).

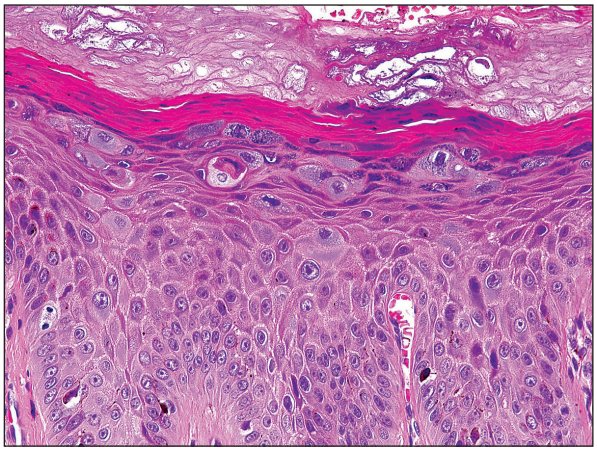

Figure 13. Epidermodysplasia verruciformis. Enlarged keratinocytes with typical granular blue-gray cytoplasm in the upper layers of the epidermis.

becoming an epidemic and is refractory to treatment.

Finally, histological EV-like changes may be seen as an incidental finding, mainly in elderly patients (39).

Histologically, EV is characterized by hyperkeratosis, hypergranulosis, and acanthosis. The most striking and characteristic feature is the presence of enlarged keratinocytes with a blue-gray granular cytoplasm, which are typically located in the upper spinous and granular layers (Figure 13). Some of these cells may be vacuolated, and they may be arranged in clusters. The lesions may progress with gradually more pronounced cytological atypia, which may eventuate in squamous-cell carcinoma in situ, with risk of progression to invasive carcinoma in 30 to 50% of cases (1).

Conclusions

HPVs are among the most common infectious agents in humans, and can be associated with a variety of cutaneous manifestations. Awareness of this protean spectrum of clinical manifestations, of the possible complications associated with them (especially the risk of malignant transformation in some settings), and basic knowledge about the currently available diagnostic methods provide the essential means for appropriate management of these patients.

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