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Tissue-based classification of HPV infections of the uterine cervix and vagina (mucosal HPV infections)

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Summary

Terminology of HPV infections of the uterine cervix and vagina is somewhat confusing, with various terms having different meanings to different authors. This prompted us to revise the current terminology and propose a "tissue-based" classification of HPV infections of the cervix and vagina (mucosal HPV infections), which is based on histological appearance of the lesions and should be clear-cut in everyday practice of managing these patients. We hope the proposed nomenclature may overcome some of the confusion and controversy that exist in the current terminologies describing these lesions.

Key words: HPV infections; Uterine cervix; Vagina; Classification; Tissue-basis.

Introduction

Terminology of the diseases caused by the human papillomavirus (HPV) is somewhat controversial. Various terms have been used in the literature, some of them with different meanings by different authors [1]. Precise definitions and uniform terminology [2], however, are essential in comparing results of research, diagnosis and treatment of HPV infections.

Commonly used terms pertaining to classification of HPV infections

Terminology of diseases invariably includes common terms in defining specific entities. Such terms connected with HPV infection terminology are listed in alphabetic order.

Atypia "the condition of being irregular or not conforming to type". *Atypical* "irregular, not conformable to the type".

Condyloma (plural: condylomas, condylomata) "is defined as a warty growth on the skin or a mucous membrane" [3]. Mucosal condylomas may be exophytic (condyloma acuminatum) or flat (flat condyloma, condyloma latum) lesions [1, 2]. Condyloma acuminatum is also called genital, acuminate or veneral wart. Condyloma latum, instead, is a characteristic cutaneous manifestation of secondary syphilis, but on the mucosal epithelium. Giant condyloma (Buschke-Löwenstein tumor) is another cutaneous condylomatous lesion [4].

Dysplasia is defined as "1) abnormality of development, 2) in pathology, alteration in size, shape, and organization of adult cells"; *dysplastic* "marked by dysplasia" [3]. The WHO definition of dysplasia is the following: a lesion in which part of the thickness of the epithelium is replaced by cells showing varying degrees of atypia and it is further graded as mild, moderate and severe. In other words, dysplasia is an epithelial abnormality that represents a precancerous lesion. The term dysplasia has gained a widespread use in the common language of histopathology [5]. Included in this terminology is carcinoma in situ (CIS), which represents the immediate precursor of an invasive cancer [5].

Intraepithelial neoplasia indicates the presence of abnormal cells inside the epithelium but without evidence of stromal invasion. Originally introduced to describe cervical cancer precursors (cervical intraepithelial neoplasia, CIN has been divided into three grades according to the extent of epithelium occupied by the atypical cells [6].

Latent "concealed; not manifest, potential, dormant, quiescent" [3].

Latent viral infection in general represents cases where viral genome is present in clinically and morphologically normal epithelium. This applies to HPV as well, implicating cases where HPV genome is detected in histologically normal biopsies or in scrapes with no cytological abnormality [1, 2, 4].

Neoplasm "any new and abnormal growth; specifically a new growth of tissue in which the growth is uncontrolled and progressive". Called also tumor. *Neoplasia* "the formation of a neoplasm". *Neoplastic* pertaining to a neoplasm/neoplasia [3].

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Subclinical means a condition 'without clinical manifestation', i.e., an early stage of any infection and/or disease, which causes no symptoms and signs and cannot be detected by clinical diagnostic techniques.

Transformation "at the cellular level indicates change that a normal cell undergoes as it becomes malignant; in a wider sense: change of form or structure; conversion from one form to another" [3]. *Transforming* cellular change towards malignant cell phenotype.

Considerations of current terminology of HPV infections

Latent HPV infection

In latent HPV infections, viral DNA is present in the cells without any signs of cytopathic effects (CPE) of the virus, i.e., in morphologically normal epithelium [1, 2, 4]. This can only be detected by molecular methods (DNA technology, mostly by PCR). There appears to be a general consensus regarding this term.

Subclinical HPV infection (SPI)

The term subclinical HPV infection is used in different meanings by different authors [1, 2, 4], including:

– all lesions visualized by the naked eye only after the application of acetic acid;

– lesions that are not visible on routine inspection, but become visible on colposcopy after acetic acid, and which on histology contain typical HPV-induced changes;

– lesions equivalent to a flat condyloma;

– lesions which become visible only by colposcopy after acetic acid, and which on light microscopy show minor epithelial changes not consistent with typical flat condylomas [1, 2, 4];

In the strictly virological sense, the term subclinical per se implies viral infection, which has no clinical manifestation and cannot be detected by clinical means. **The morphological criteria of subclinical HPV infections are ill defined and not reproducible. Because all the above listed options necessitate detection of something by any of the clinical tools (colposcopy, acetic acid, or histology), none of these definitions for subclinical HPV are compliant with the strict virological definition.**

Cervical intraepithelial neoplasia (CIN)

CIN is cervical cancer precursor of squamous epithelial origin, characterized by the presence of atypical cells within the epithelium but with no stromal invasion [6]. Three grades of CIN exist, known as CIN1, CIN2 and CIN3. This term superseded the old terminology of mild, moderate and severe dysplasia and CIS, introduced in the early 1950s [5]. The concept of dysplasia-CIS was the first classification used to categorize the process of cervical carcinogenesis on light microscopy [5, 7]. The advantage of the CIN classification is that it clumps together the severe dysplasia and CIS lesions, the distinction of which is highly arbitrary and poorly reproducible. The concept of CIN terminology included that all degrees of the abnormal intraepithelial changes should be given the same name, representing the continuous spectrum of the disease [6]

Squamous intraepithelial lesion (SIL) is a term introduced by the Bethesda System (TBS) to replace the term cervical intraepithelial neoplasia (CIN) [8, 9]. SIL represents a precancerous condition where normal epithelial cells are replaced by abnormal cells; classified as high grade (HSIL) or low grade (LSIL). Actually, this term is used to describe squamous cell abnormalities for cytology, and it should not be used to describe histopathological changes [8, 9].

Carcinoma in situ (CIS) is an intraepithelial lesion of the most severe grade, the immediate precursor of true carcinoma [5, 7]. CIS is the most severe category of the dysplasia-CIS nomenclature used to classify the precancer lesions and it is included in the CIN terminology as CIN3 [1, 8, 9].

Atypical metaplasia represents an epithelial change also known as atypical reserve cell hyperplasia. This term should be reserved only for the thin metaplastic epithelium that shows cellular atypia from the very beginning (1). This change has been regarded by some as the earliest manifestation in the development of a CIN lesion (10). According to most authorities, it is not a distinct entity, however.

Cervical squamous cell carcinoma (SCC)

This is the main histological type of cervical carcinoma, so named because of its origin from squamous cells. Unless otherwise defined, the general term cervical cancer usually denotes squamous cell carcinoma.

Cervical glandular intraepithelial neoplasia (CGIN)

These are the precursor lesions for cervical adenocarcinoma [11, 12]. Currently, two grades of glandular precancer lesions are differentiated; low-grade and high-grade. The latter are equivalent to adenocarcinoma in situ (AIS) [13], whereas low-grade lesions denote all lesions with less severe atypia than AIS.

CGIN is another name to describe cervical glandular intraepithelial neoplasia, which is characterized by the presence of atypical columnar cells [14, 15]. Three grades are described: CGIN I, the equivalent of mild dysplasia, CGIN II, the equivalent of moderate dysplasia and CGIN III, the equivalent of AIS. Today this designation is decreasingly used, because of the problems in reproducibility [12, 14, 15].

AIS is the immediate precursor of cervical adenocarcinoma [11-13]. Histologically, the changes of AIS are those described for CGIN, at their most accentuated form [11, 12]. The affected glands show abnormal architecture with intraluminal papillary projections, with or without stromal cores, cribriform areas, outpouchings and back to back arrangement of the glands. To meet the criteria of AIS, the basement membrane must be intact and a compact surrounding stroma should be detectable around the atypical glands [11-13]. Not unlike CGIN, different subclassifications have been introduced for AIS as well [14, 15]. The most recent one divides AIS into four subcategories according to their cell type: 1) endocervical cell type, 2) endometrioid type, 3) intestinal type, and 4) miscellaneous type. The histogenetic validity and general applicability of such subclassifications have been questioned, however [11, 12].

Cervical adenocarcinoma

This is the other main histological type of cervical cancer, arising from the glandular tissue of the endocervix. A large number of different histological subtypes of cervical adenocarcinoma exist, some with substantial prognostic implications [12].

Vaginal intraepithelial neoplasia (VAIN)

VAIN nomenclature is used to grade the precursor lesions of vaginal squamous cell carcinoma [16, 17]. Originally, three grades of VAIN were distinguished, but more recently the division into low-grade and high-grade VAIN has gained more popularity, due to the difficulties in categorizing the intermediate (VAIN II) grade of lesions with any feasible degree of reproducibility [18].

Vaginal squamous cell carcinoma

Albeit a rare disease, this is the most common type of the primary vaginal carcinomas and it seems to be related to HPV infections [4]. Compared with other genital SCCs, the number of vaginal carcinomas analyzed for HPV is still too small to draw definite conclusions. Until further confirmatory data are available, it seems reasonable to conclude that the evidence linking HPV with the development of vaginal cancer is fairly suggestive, but not as firm as established for cervical cancer. Similarly, the suggested concept on vaginal carcinomas with two different etiologies (HPV-related and non-HPV-related) remains to be elucidated [4].

Condyloma acuminatum

Condyloma acuminatum is an exophytic lesion characterized by numerous fine, finger-like epithelial projections (papillomatosis), which consists of acanthotic epithelium with koilocytosis and a connective tissue core containing a capillary loop [1, 2, 4]. Para-, hyper- or dyskeratosis is common. Persistent acetowhite change occurs after acetic acid application, which also causes the papillae to retract and separate and may mask fine vascular patterns.

Atypical condyloma

Occasionally condyloma acuminatum is associated with abnormal vessels with various shape and caliber, some showing staghorn-like appearance [19] and elongated and enlarged nuclei with anisokaryosis, pyknosis and atypical mitotic figures. Dysplastic cells, however, are absent. This is called atypical condyloma by some authors [19], but is regarded as a benign lesion associated with HPV6/11 genotypes [1, 2, 4].

Flat condyloma

Flat condylomas are acanthotic epithelial lesions with abundant koilocytes in the upper cell layers usually covered by para- or hyperkeratosis [1, 2, 4]. Histologically three types of flat condylomas can be distinguished, such as typical, spiked and endophytic flat condylomas. The spiked condyloma is built up of tiny epithelial projections (spikes or asperities), but it is not exophytic [1, 2, 4]. **Typical sites include the vagina where the lesions can be multiple, and vulva where the lesions are also called microcondyloma or filamentous condyloma [20].** Endophytic condylomas occur exclusively on the uterine cervix and grow towards connective tissue and endocervical glands, giving the lesion an inverted appearance. Not infrequently, the histopathological features of the various types are encountered in the same lesions [1, 2, 4].

Flat condylomas are most often large with marked, geographic borders and situated in or around the transformation zone. They are acetowhite with fine punctation and fine mosaic patterns in most cases, however, bizarre vascular patterns are not exceptional. Their surface is smooth with the exception of the spiked condyloma with a slightly uneven surface contour. Acetowhite reaction is often slow but may be dense. When keratosis is prominent, the lesion may be raised. They are iodine negative. Flat condylomata are hard to distinguish colposcopically from low-grade CIN; actually they are included in the category of low-grade lesions by TBS [8, 9]. Another characteristic colposcopic appearance of flat condylomas is the brain-like surface counter, i.e. corrugation and convolution forming ridges.

Characteristically, all types of condylomatous lesions share common histopathological features: they are acanthotic epithelial lesions with abundant koilocytes in the intermediate and superficial layers. Hyper- para- or dyskeratosis is common, and slight proliferation of the basal and parabasal cells may be encountered. Other features include frequent multinucletion, and slightly increased mitotic figures [1, 2, 4, 20]. Basically, mucosal condylomas differ in their tissue architecture only. By definition, however, benign condyloma lesions are devoid of dysplastic cells.

Proposed classification of genital mucosal HPV infections

The proposed classification of cervical and vaginal (genital mucosal) HPV infections is shown in Table 1.

Table 1. — *Tissue-based classification of HPV infections of the cervix and vagina (mucosal HPV infections).*

Latent HPV infection
Subtle HPV infection
Transforming HPV infections
– Cervical intraepithelial neoplasia (CIN)
– Cervical squamous cell carcinoma
– Cervical glandular intraepithelial neoplasia (CGIN)
– Adenocarcinoma in situ (AIS)
– Cervical adenocarcinoma
– Vaginal intraepithelial neoplasia (VAIN)
– Vaginal squamous cell carcinoma
Non-transforming HPV infections
– Condyloma acuminatum
– Flat HPV infections (typical flat, spiked and endophytic condylomas)
– Atypical condyloma
Mixed HPV infections
– Flat HPV infections with co-existent or combined neoplastic epithelial changes

1) The vast majority of cervical/vaginal HPV infections regress unnoticed, most of them without causing any cytopathic effect, i.e., without any epithelial abnormality. This is called *latent HPV infection* and it is an entity distinct from the clinical HPV lesions [1, 2, 4].

2) Not infrequently, minor cellular abnormalities subtle enough to raise only a suspicion of HPV infection are detected on histology and/or in cervical smear. These lesions contain the HPV genome and can be slightly acanthotic. The bulk of the epithelial thickness is composed of intermediate cells with usually slightly vacuolized cytoplasm, raising the suspicion of koilocytosis. However, when strictly evaluated, these cells lack the marked nuclear changes characteristic to genuine HPV-induced koilocytosis (Figure 1). Few mitotic figures and slight para- or hyperkeratosis may occur. These lesions are best called *subtle HPV infection*.

Thus, by definition, *subtle HPV infections* are epithelial lesions that on light microscopy raise a suspicion of HPV infection. By definition, such lesions are devoid of any dysplastic changes and also lack characteristic koilocytes. When studied with sensitive HPV detection methods (e.g., PCR or tyramine-amplified ISH) [1] they contain HPV DNA, however. Appearance on light microscopy can be variable, but slight hyper- or parakeratosis, acanthosis and intermediate cell vacuolization are usually present (Figure 1). The natural history of such lesions is unknown, justifying their inclusion as a separate entity within the spectrum of HPV infections.

3) HPV infection with frank epithelial abnormalities can be separated into two groups: a) those with the potential of progressing to cancer and b) those which are benign. The former may be called dysplastic, neoplastic or transforming lesions, while the latter as non-dysplastic, non-neoplastic or non-transforming abnormalities.

By definition, 'dysplasia' – as discussed above – is a general term of disordered form or differentiation, but in oncology, it is used in the context of atypia and carcinogenesis. It is a widely used expression. In cervical pathology, however, the term dysplasia [5, 7] has been replaced by cervical intraepithelial neoplasia (CIN) [6].

Fig. 1

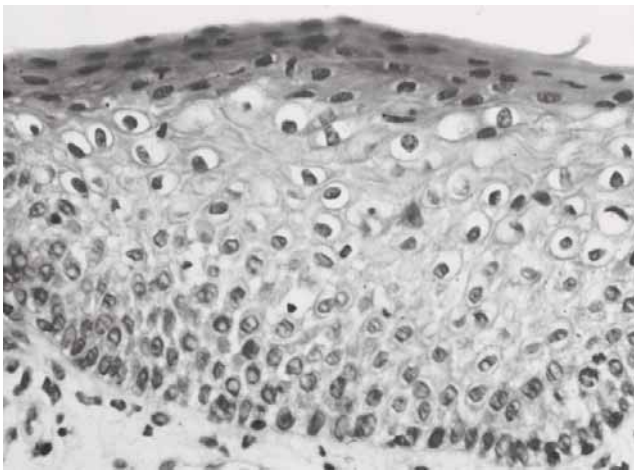


Fig. 2

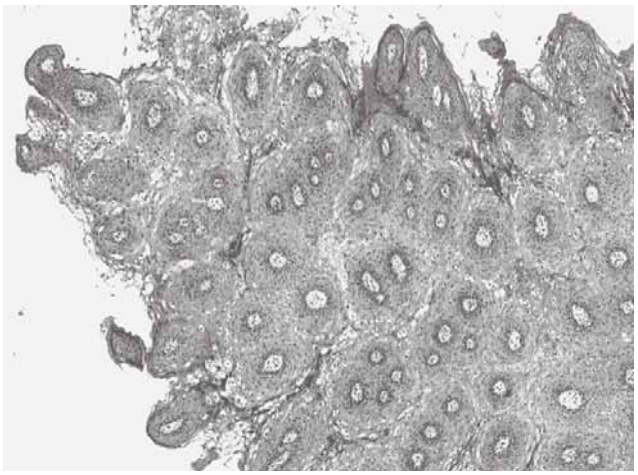


Fig. 3

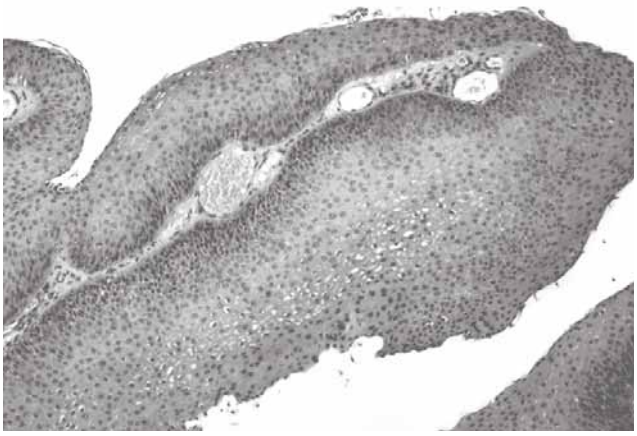


Fig. 4

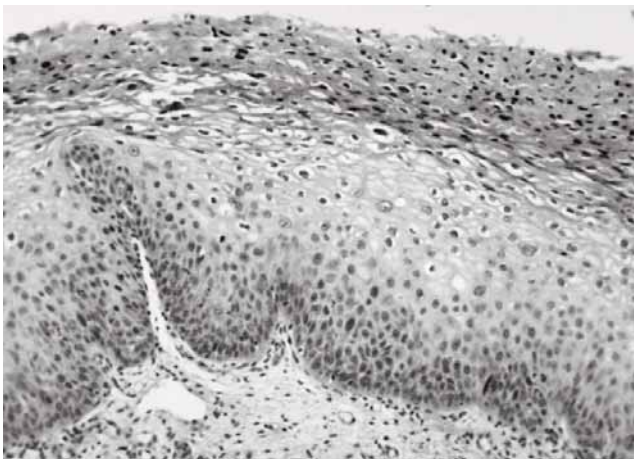


Fig. 5

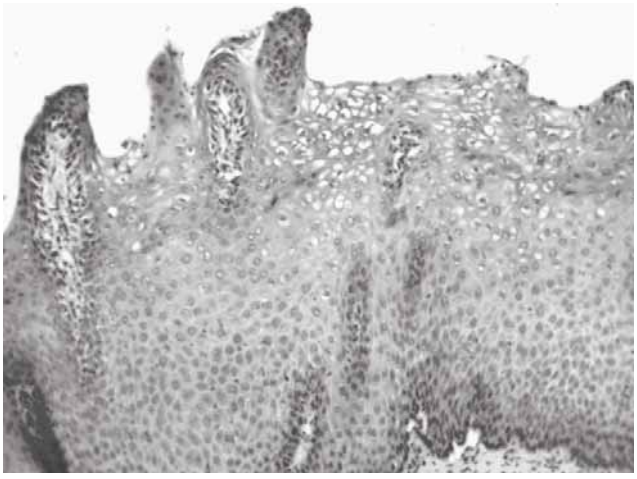


Figure 1. — Subtle HPV infection. In this flat lesion, many features raising the suspicion of HPV infection are present, including slight parakeratosis, vacuolization of epithelial cells in the uppermost intermediate layers as well as some proliferative activity of parabasal cells. This particular lesion tested positive for HPV42 in ISH analysis. (HE, original magnification x 250).

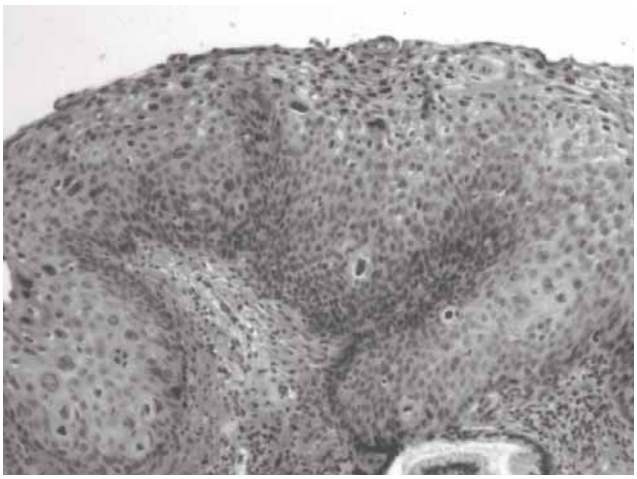
Figure 2. — Condyloma acuminatum of the uterine cervix presenting with all typical features; papillomatosis, acanthosis, para/hyperkeratosis and koilocytosis. There is no epithelial atypia in this benign lesion, which proved to contain high copy numbers of HPV6. (HE, original magnification x 40).

Figure 3. — A medium power detail of a lesion diagnosed as an atypical condyloma. One of the numerous papillary structures with a connective tissue core is presented. Numerous dilated capillaries are present which on colposcopy gave an impression of atypical vessels. Koilocytes are detected in the intermediate layers, and some degree of atypia also in the basal/parabasal cells (upper part of the papilla). HPV11 was detected and the lesion was considered as benign. (HE, original magnification x100).

Figure 4. — Flat condyloma in its most typical presentation. The epithelium has a completely flat surface, is clearly acanthotic and contains all characteristic morphological features of HPV infection. There is a thick layer of parakeratotic cells, overlying the intermediate layers with koilocytotic cells. Many of the latter are bi- or multinucleated. There is also some hyperplasia in the parabasal cells, but the basal layer is regular, with no signs of dyslasia. HPV11 was detected. (HE, original magnification x 100).

Figure 5. — Another variant of a flat condyloma known as spiked condyloma. An otherwise morphologically flat lesion contains numerous small spikes or asperities composed of a thin squamous epithelium supported by a tiny connective tissue core with small capillaries. Koilocytes are abundantly present in superficial layers and the basal cell layer is regular, with no signs of dysplasia. This lesion tested HPV6 positive in ISH. (HE, original magnification x 100).

Fig. 6



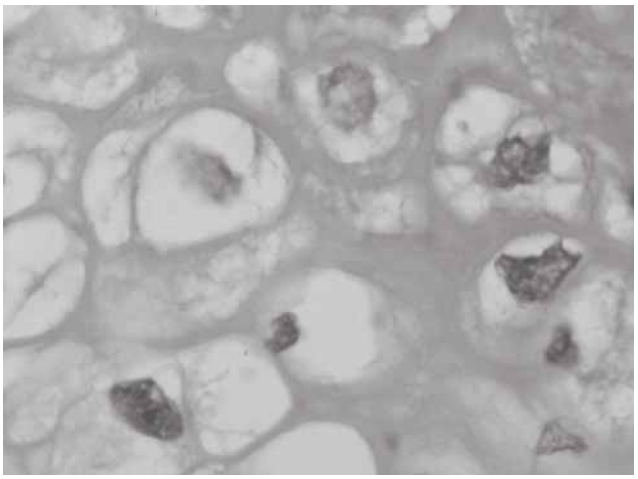


Fig. 7

Figure 6. — Another variant of a flat condyloma called endophytic condyloma. This lesion has a flat epithelial contour with no spikes. The acanthotic epithelium contains numerous koilocytes as well as bi- and multinucleated cells. In this rapidly growing lesion, many mitotic figures and apoptotic bodies are found as well. The characteristic feature is the inverted (endophytic) type of growth, when the epithelium shows penetration into the underlying gland openings and also pushing to connective tissue stroma. In most part of the lesion, a single row of basal cells is seen except in the center, where signs of mild dysplasia are seen. This lesion was HPV18 positive. (HE, original magnification x 100).

Figure 7. — The common feature characteristic to all condyloma lesions irrespective of their morphology: koilocytes, photographed with the highest resolution that light microscope can reach. With this power, all characteristic features of this cytopathic effect of HPV become discernible. The cytoplasm is vacuolized, and condensed towards cell periphery. Inside the cytoplasm, one can distinguish filamentous structures that represent collapsed and fragmented intermediate filaments (IF). Nuclei are enlarged and hyperchromatic, sharply angulated and chromatin is unevenly distributed. In some cells, also the nucleoli are clearly visible. (HE, original magnification x 1000).

The term ‘transforming epithelial changes’ is invariably related to malignancy, but the word ‘transformation’ in cervical histology is mostly connected to the area of squamous cell metaplasia, called transformation zone (TZ) [2, 10].

The adjective ‘neoplastic’ is pertaining to tumor growth and precursor lesions of the uterine cervix and the vagina; actually the precursor lesions bear this word in their name (cervical/vaginal intraepithelial neoplasia) [1, 4, 6, 16, 17]. Thus, the expressions of *neoplastic HPV infections* and *non-neoplastic HPV infections* might appear to be the most appropriate. One can always argue, however, whether a benign condyloma should also be considered as a neoplasia or not. If the former view is favored, then the two categories here should be equally well called as *transforming* and *non-transforming* HPV infections [1, 2, 4, 20]. Instead of a pure morphologic meaning (neoplastic vs non-neoplastic), these two terms include a value judgment; one assumes that transforming inevitably means equivalent to malignant, while non-transforming implicates an invariably benign lesion.

The transforming HPV lesions are listed in Table 1.

As for *non-transforming HPV infections*, the designation ‘condyloma acuminatum’ (Figure 2) and that of its atypical counterpart (atypical condyloma) (Figure 3) is well defined. However the term ‘flat condyloma’, albeit is widely used, is clearly an unfortunate misnomer [1, 4, 10, 19]. As discussed above, condyloma per se means a warty (exophytic) lesion, equivalent to squamous cell papilloma (SCP) at other mucosal sites [1, 4, 20] (Figure 2). Actually, in the older literature, some authors used SCP and condyloma as synonyms while describing cervical lesions [21]. Therefore, the name flat condyloma gives an impression of something that is at the same time exophytic (condyloma) and flat, which is highly confusing. In its most typical appearance, flat condylomas are acanthotic epithelial changes with smooth surface, with nothing that points to warty or exophytic growth (Figure 4). As pointed out above, however, there are subtypes of flat condyloma that show some warty features while presenting with tiny spikes or asperities on the surface of an otherwise flat (= laterally spreading) lesion (Figure 5). This is in strong contrast to genuine condylomata acuminata, which demonstrates an exophytic (= vertical) growth, with very little lateral extension and sometimes is connected to underlying epithelium with a narrow string (= base) of connective tissue stalk only (Figure 2).

If we stick to the original definition of condyloma, these flat HPV lesions cannot be adequately characterized by calling them as flat condyloma. We need to abandon the expression “condyloma” here and replace it by another expression. Potential options are: infection, lesion or growth, i.e., *flat HPV infections* or *flat HPV lesions or flat HPV growths*. For consistency with other categories, we prefer to use the name *flat HPV infections* in this context. The histological sub-

types of these flat HPV infections (flat, spiked, endophytic), represent histological variants of the same lesions, and do not represent different clinical manifestations to justify calling them as separate entities (Figures 4-6).

Irrespective of their histological morphology, whether exophytic or flat, all HPV infections share a common morphological feature, i.e., the cytopathic effect of HPV, known as koilocytosis (Figure 7). Without recognition of these cells, there is no means to make the definite diagnosis of HPV infection on light microscopic examination (1,4,19,20)

Mixed HPV infections

Mixed HPV infections are flat HPV infections with co-existent or combined neoplastic epithelial changes (Figure 6). As repeatedly pointed out, such lesions with signs of HPV infection combined with obvious dysplastic changes should be evaluated for the degree of CIN using the same criteria as applied for lesions devoid of these morphological manifestations of HPV, i.e., graded into CIN1, CIN2 or CIN3 as usual [6].

Conclusions

Common language, i.e., coherent terms and clear definitions is a prerequisite not only in basic research but in clinical practice of managing the patients as well [2]. This prompted us to revise the current terminology and propose a "tissue-based" classification of HPV infections of the cervix and vagina, which is based on histological appearance of the lesions and should be clear-cut in everyday practice of managing these patients. We hope this proposed nomenclature can overcome some of the confusion and controversies that exist in the current terminologies describing these lesions.

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