Histopathology of cervical precursor lesions and cancer

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KEY WORDS

cervical cancer, precursor lesions, cytological screening, histomorphology

ABSTRACT

The most frequent types of cervical cancer are squamous-cell carcinoma and adenocarcinoma, which develop from the distinctive precursor lesions cervical intraepithelial neoplasia (CIN) / squamous intraepithelial lesion (SIL), and adenocarcinoma in situ (AIS), respectively. Their tumorigenesis is HPV-related. High-risk HPV (e.g., types 16 and 18) is integrated into the genome and leads to tumor progression. Cytological screening leads to detection of precursors and their mimics. P16 and Ki-67 immunohistochemistry assists in the histological differential diagnosis of precursors to reactive and metaplastic epithelium. For invasive cervical carcinoma, stage is the strongest prognostic factor. Per definition, microinvasive (pT1a1 / pT1a2) carcinoma is diagnosed histologically on cone biopsies and treated less radically. The distinction between adenocarcinomas of the cervix and endometrial adenocarcinomas is important and can be supported by immunohistochemistry (e.g., ER, p16, CEA, and vimentin) and HPV in-situ hybridization. The rarer adenoid-basal and neuroendocrine carcinomas are less frequently HPV-related.

Introduction

Although invasive cervical carcinoma has become rare in most European countries, from the global perspective it must still be considered a public health burden. In particular, many countries in Africa, southeast Asia, and Latin America reveal an incidence that is more than 10 times as frequent compared to the incidence in central Europe (1). Various factors seem to be responsible for these epidemiological differences, such as socioeconomic standards, immunodeficiency, and HPV infection (2). In particular, because the pathogenesis has been clearly linked to HPV infection, cervical carcinoma has become a preventable disease.

Histologically, the most frequent type of cervical carcinoma is squamous-cell carcinoma followed by adenocarcinoma (3, 4), of which various subtypes are distinguished (Table 1). Both squamous-cell carcinoma and adenocarcinoma develop through distinctive precursor lesions. For some of the rare types of cervical carcinoma, such as adenoid-cystic, adenoid-basal, and small-cell carcinoma, no precursor lesions are known. The practical value of the precursor lesions

is their presence in cervicovaginal smears and the possibility of early detection by cytological screening. The frequency of precursor lesions has significantly increased in most European countries along with the decrease in cervical carcinoma incidence.

Pathogenesis and histomorphology of squamous-cell carcinoma and its precursor lesions

Our current understanding of the pathogenesis of squamous-cell carcinoma considers it to develop from precursor lesions designated as cervical intraepithelial neoplasia (CIN) (5). CIN is categorized into three grades (CIN1–3) based on the degree of proliferation of atypical basaloid cells (1). The atypical basaloid cell proliferation involves the basal third of the epithelium in CIN1, reaches the middle third in CIN2, and extends to the superficial third in CIN3. A more recent approach based on the Bethesda system for cervical cytology distinguishes between two categories with distinctive biology: low- and high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively). LSIL is characterized by extensive HPV-related cytological changes such as koilocytosis and proliferation of the basal and parabasal cells with mild atypia and mitosis. In contrast, HSIL consists of small to medium-sized atypical basal cells that may involve the entire thickness of the epithelium and it often lacks clearly visible HPV-related cytological changes. If compared to the WHO classification, CIN1 relates to LSIL, whereas CIN2 and 3 are related to HSIL. The various classification schemes are compared in Table 2.

From a biological point of view the dualistic Bethesda approach is reasonable because LSIL and HSIL reveal a different pathogenesis. LSIL is mostly associated with low- or intermediate-risk HPV such as HPV-6 and -11, whereas HSIL harbors clearly oncogenic HPV DNA such as types 16, 18, 31, 33, and 45. There are also fundamental differences between LSIL and HSIL effects at the cellular level (6). LSIL is characterized by infection of terminally differentiated cells that are unable to divide. Therefore the cytological changes involve only the superficial layers of the epithelium. On the other hand, HPV infection in HSIL involves the basal and parabasal cells, which are still capable of dividing. This leads to morphological changes in all or almost all layers of the epithelium. LSIL is typically characterized by low-risk HPV–induced DNA synthesis without accumulation of abnormal DNA, whereas HSIL shows the latter as the consequence of a disrupted cell cycle by high-risk HPV. This leads to aneuploid cells that are able to replicate and survive. The mechanism responsible for this process in HSIL is mainly induced by the viral proteins E6 and E7 and further involves host regulatory proteins such as cyclins, cyclin-dependant kinases, and cyclin-dependant kinase inhibitors. This leads to deregulation of the cell cycle and the apoptotic pathway. Important apoptotic proteins such as p53 and Rb lose their function and others such as p16 are deregulated. HSIL is further characterized by in-

Table 1. WHO classification of malignant tumors of the uterine cervix and their precursors, modified according to (1).

Epithelial tumors
Squamous tumors and precursors
Squamous-cell carcinoma, NOS
Keratinizing
Non-keratinizing
Basaloid
Verrucous
Warty
Papillary
Lymphoepithelioma-like
Squamotransitional
Early invasive (microinvasive) squamous-cell carcinoma
Squamous intraepithelial neoplasia
Cervical intraepithelial neoplasia (CIN3)
Squamous-cell carcinoma in situ
Glandular tumors and precursors
Adenocarcinoma
Mucinous adenocarcinoma
Endocervical
Intestinal
Signet-ring cell
Minimal deviation
Villoglandular
Endometrioid adenocarcinoma
Clear cell adenocarcinoma
Serous adenocarcinoma
Mesonephric adenocarcinoma
Early invasive adenocarcinoma
Adenocarcinoma in situ
Glandular dysplasia
Other epithelial tumors
Adenosquamous carcinoma
Glassy cell carcinoma variant
Adenoid cystic carcinoma
Adenoid basal carcinoma
Neuroendocrine tumors
Carcinoid
Atypical carcinoid
Small-cell carcinoma
Large-cell neuroendocrine carcinoma
Undifferentiated carcinoma

Table 2: Comparison of different classification systems of precursor lesions of cervical squamous-cell carcinoma.

Traditional classification	WHO classification	Bethesda classification
Mild dysplasia	CIN1	LSIL
Moderate dysplasia Severe dysplasia Carcinoma in situ	CIN2 CIN3	HSIL

CIN = cervical intraepithelial neoplasia; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion.

tegration of the viral DNA into the host genome whereas LSIL shows an episomal location of HPV DNA. LSIL associated with low-risk HPV is usually polyclonal, whereas those associated with high-risk HPV tend to be monoclonal (7). Most HSIL are monoclonal but polyclonality may occur. There is some evidence that polyclonal lesions tend to regress whereas monoclonal lesions show progression (8).

There is evidence that only a subset of CIN1/LSIL progresses into CIN2 and 3/HSIL because most LSIL have the potential to regress over some years (9). It is unclear whether all CIN3 develop from CIN1 but it has been hypothesized that CIN3 originates "de novo" from metaplastic squamous epithelium under the transition of atypical squamous metaplasia. However, this has not been proven at all. One further problem is that atypical squamous metaplasia cannot be easily distinguished from CIN3 and shows poor interobserver agreement even among experts.

The hallmark of LSIL/CIN1 is moderate-to-marked nuclear atypia on the surface of the epithelium (10). Keeping this in mind helps avoid overdiagnosis. In addition, LSIL is very rare in postmenopausal women. Non-atypical cells with perinuclear halos do not qualify for koilocytosis and are instead designated "pseudokoilocytes." Furthermore, LSIL/CIN1 usually do not harbor a lot of mitosis and abnormal mitotic figures. Therefore, lesions with a high mitotic index must be upgraded to HSIL. With respect to HSIL, its variable histological presentation must be stressed. HSIL may be associated with marked koilocytosis, hyperkeratosis or even metaplastic features. Reflecting the multipotential nature of transformation zone cells, HSIL may even combine squamous and mucinous features.

Differential diagnosis includes metaplastic and reparative processes as well as atrophy (10). Criteria that help on H&E sections are loss of polarity, distribution of chromatin, mitosis and, in particular, nuclear polymorphism. Furthermore, most non-neoplastic lesions tend to show maturation on the epithelial surface.

Among various biomarkers, p16 and Ki-67 seem to be useful for differential diagnosis of intraepithelial neoplasia of the cervix (11). P16 overexpression has been linked to continued expression of the viral oncogene E7 due to HPV infection of the epithelium (12). Therefore, a diffuse strong p16 staining of squamous epithelium points to infection by high-risk HPV and may occur in HSIL and up to 35 to 50% of LSIL (13). The diagnosis of a lesion is further supported by a high Ki-67 labeling index with many Ki-67 positive nuclei within the superficial half of the epithelium. However, it has to be kept in mind that both LSIL/CIN1 and metaplastic epithelium may show focal, patchy staining for p16.

Invasive squamous-cell carcinoma and the significance of microinvasion

Invasive squamous-cell carcinoma consists of nests and irregular clusters of tumor cells, which may show either a basal-like appearance or maturation, often with keratinization. Keratin formation is considered a sign of good differentiation. Today a sub-classification into keratinizing and non-keratinizing squamous-cell carcinoma is recommended, in particular to avoid confusion of small-cell squamous carcinoma and small-cell carcinoma of neuroendocrine type. Neither histopathological grading nor keratinization seems to influence prognosis. The strongest prognostic factor is tumor stage, which is particularly reflected by the issue of microinvasive carcinoma.

Microinvasive carcinoma is defined by size in

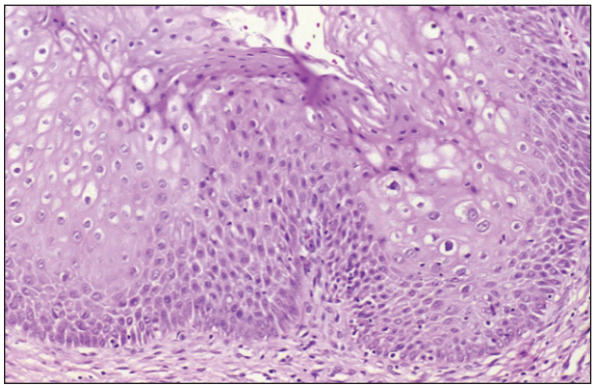

Figure 1. Cervical intraepithelial neoplasia 1 (CIN 1) / low-grade intraepithelial lesion (LSIL). The epithelial changes are characterized by significant nuclear atypia in the superficial half due to extensive koilocytosis and proliferation of basal and parabasal cells. The mitotic index is low. HE, 100×.

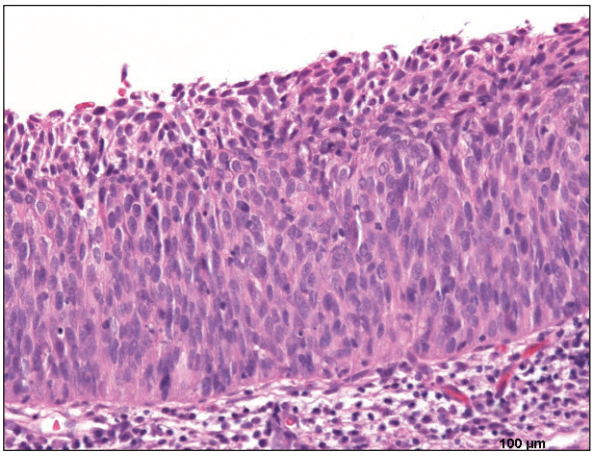

Figure 2. Cervical intraepithelial neoplasia 3 (CIN 3) / high-grade intraepithelial lesion (HSIL). The epithelium lacks maturation and consists of small highly atypical cells with hyperchromatic nuclei. HE, 100×.

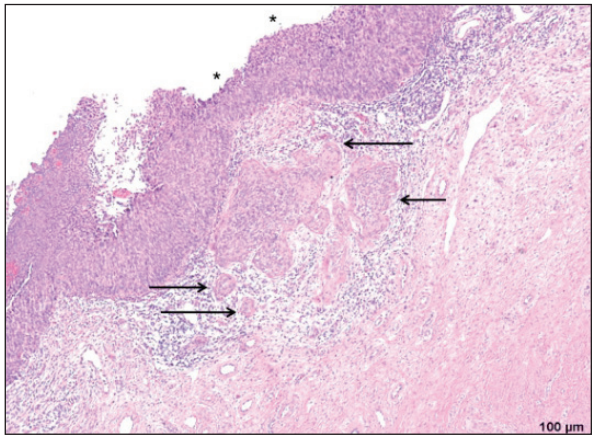

Figure 3. Microinvasive squamous-cell carcinoma of the cervix (pT1a1), diagnosed on a cone biopsy. Small irregular nests of well-differentiated squamous carcinoma invade the cervical stroma from glands (crypts) (arrows). The surface is covered by CIN3 (asterisks). HE, 20×.

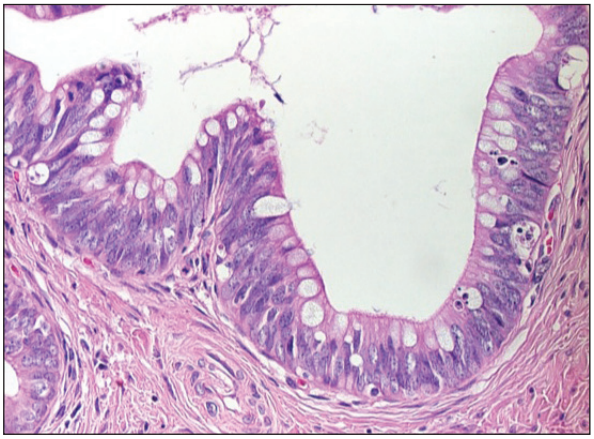

Figure 4. Adenocarcinoma in situ (AIS). Endocervical glandular epithelium is replaced by pseudostratified atypical epithelium with goblet cells. HE, 200×.

the absence of a clinically visible tumor (14). By definition, microinvasive carcinoma is diagnosed histologically and thus detected through the histopathological analysis of cone biopsies from patients with CIN3. The current FIGO and UICC classification for cervical carcinoma staging (Table 3) defines microinvasive carcinoma by a maximum horizontal dimension of 7 mm and subdivides two categories with a maximum vertical diameter of 3 mm (Ia1) and 5 mm (Ia2), respectively (14, 15). The measurement is taken from the base of the epithelium, either on the surface or within a gland (crypt) from which the tumors originate (16). The subcategorization of microinvasive carcinoma has important therapeutic repercussions because cone biopsy or simple hysterectomy is usually sufficient for pT1a1/Ia1 tumors.

For the histological diagnosis of microinvasive carcinoma of the cervix, penetration of tumor cells through the basement membrane is required. Invasive foci of tumor cells are usually arranged in a haphazard

Table 3. TNM and FIGO classification of cervical carcinoma (14).

pTNM categories (pT = primary tumor)	FIGO stages	Description
PTis	**0**	Carcinoma in situ (preinvasive)
pT1	**I**	Cervical carcinoma confined to the uterus
pT1a	IA	Diagnosed only by microscopy
PT1a1	IA1	Depth ≤ 3mm, horizontal spread ≤ 7mm
PT1a2	IA2	Depth ≤ 5mm, horizontal spread ≤ 7mm
pT1b	IB	Clinically visible or microscopic lesion > pT1a2
PT1b1	IB1	Tumor diameter ≤ 4cm
PT1b2	IB2	Tumor diameter > 4cm
pT2	**II**	Tumor infiltrates beyond the uterus but not to the pelvic wall or to the lower third of the vagina
pT2a	IIA	No parametrial involvement
PT2a1	IIA1	Tumor diameter ≤ 4cm
PT2a2	IIA2	Tumor diameter > 4cm
pT2b	IIB	Infiltration of the parametrium
pT3 and/or N1	**III**	Tumor infiltrates to the pelvic wall, to the lower third of the vagina or is associated with hydronephrosis
pT3a	IIIA	Lower third of the vagina
pT3b	IIIB	Infiltration to the pelvic wall or hydronephrosis
pN1	IIIB	Metastases in pelvic and/or para-aortic lymph nodes
pT4	IVA	Tumor infiltrates mucosa of rectum or urinary bladder or beyond true pelvis
pN – Regional lymph nodes		
pNx		Regional lymph nodes cannot be assessed
pN0		No metastases in regional lymph nodes
pN1		Metastases in regional lymph nodes
pM – Distant metastases		
pMx		Distant metastases cannot be assessed
pM0		No distant metastases
pM1	IVB	Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease; excludes involvement of vagina, adnexae, and pelvic serosa)

pattern and show irregular margins. They usually display better differentiation than the associated CIN by showing maturation. The use of immunohistochemistry to demonstrate stromal invasion is of limited value. In particular, disruption of the basement membrane as demonstrated by loss of laminin and collagen IV, respectively, may also occur in normal crypts and CIN.

If microinvasive carcinoma occurs multifocally, the extent of the largest focus is used for classification. This has been challenged by studies that are based on volumetric measurement of tumor size (17). Because small pT1b1/IB1 carcinomas may occur without a clinical visible tumor and be associated with excellent prognosis, expanding the microinvasive carcinoma category has been suggested (18).

Various special types of squamous-cell carcinoma have been described, which are rare and thus of limited clinical value.

Pathogenesis and histomorphology of adenocarcinoma and its precursor lesions

In contrast to squamous-cell carcinoma, the precursor lesion of adenocarcinoma, adenocarcinoma in situ (AIS), is not further subdivided (1). AIS is characterized by cellular atypia similar to colorectal adenoma and may show a variety of cellular differentiation including goblet cells. The nuclei are usually cigar-shaped and pseudostratified, showing coarse chromatin and numerous mitoses. Glandular dysplasia, a lesion with less pronounced changes compared to AIS, has been suggested as a precursor to AIS but has been challenged due to its poor reproducibility and, in particular, its negligible clinical value (19, 20). Recently, a scoring system was proposed to distinguish between glandular dysplasia and AIS but due to its limited clinical value it has been suggested that the term "glandular dysplasia" no longer be used in the clinical setting (21). The term CGIN (cervical glandular intraepithelial neoplasia), which is subdivided into three grades, is used in the UK but not in the U.S. and continental Europe. The differential diagnosis of AIS includes reactive changes of the glandular endocervical epithelium and tubal metaplasia. P16 and Ki-67 immunohistochemistry is useful but it needs to be emphasized that tubal metaplasia shows focally strong p16 immunoreactivity (22).

Cervical adenocarcinoma shows a variety of histological patterns (1). If various histological components are present in one tumor, the classification should be based on the predominant pattern, and the other pattern, if present in at least 10% of the tumor, should just be mentioned in the report (16). The most frequent histological types are the endocervical type, mucinous adenocarcinoma, and endometrioid adenocarcinoma (23). There are divergent reports on the distribution of these two histological types, ranging from a twice-as-frequent incidence of the endocervical type compared to endometrioid adenocarcinoma to a slight predominance of endometrioid adenocarcinoma. More striking is the change in the proportion between adenocarcinoma and squamous-cell carcinoma of the cervix. Cancer registries of several countries have reported a relative increase in the ratios of adenocarcinomas compared to squamous-cell carcinomas. In some countries the incidence of invasive cervical carcinoma decreased from the 1970s to the 1990s by up to one-third, whereas the incidence of adenocarcinoma increased by up to 30% (24).

Association with HPV has been found for virtually all types of adenocarcinoma of the cervix, although some data are controversial. Mucinous and endometrioid adenocarcinomas frequently harbor HPV DNA 16 (50%) and 18 (40%) and, less frequently, 45 (25%). In contrast to previous findings, HPV DNA was recently also found in adenocarcinoma by using new technologies (26).

Microinvasive adenocarcinoma

A category of microinvasive adenocarcinoma has also been established but, in contrast to its squamous-cell counterpart, the diagnosis is more difficult and has been controversial. Basically all histological types of adenocarcinoma may be found in this category but small pT1a/IA tumors are much rarer compared to the squamous-cell carcinoma group. The most important diagnostic criterion, stromal invasion, is not always unequivocally visible in small glandular lesions of the cervix. In particular, well-differentiated and superficially located glandular lesions may be difficult to diagnose. A marked glandular irregularity with haphazardly arranged glands is considered an indication for an infiltrative growth. Recently, the close relationship of glands to blood vessels was assessed as a diagnostic tool for invasive carcinomas (27). A desmoplastic inflammatory stromal response may be of further help and the presence of lymph vascular invasion confirms the carcinoma diagnosis (1). Less difficult to diagnose is a confluent glandular pattern with loss of stroma and formation of cribriform tumor areas or a complex papillary pattern. The vertical diameter of the tumor is usually measured from the surface of the lesion, reflecting tumor thickness rather than the true depth of invasion (28). The prognosis of microinvasive adenocarcinoma is excellent (29).

Adenosquamous carcinoma

Adenosquamous carcinoma, defined as a tumor with both squamous and glandular differentiation, may account for 5 to 20% of all cervical carcinomas, but its diagnosis varies and is controversial. It was categorized among mixed carcinomas but the recent WHO classification considered it a distinctive type (1). The squamous component may even show keratinization but for the diagnosis a sufficient formation of glands must be present. Endometrioid adenocarcinomas with benign-looking squamous elements must not be called adenosquamous carcinomas. It is likely that by using strict diagnostic criteria the number of adenosquamous carcinomas may decrease significantly. Due to similar epidemiologic risk factors and prognosis, adenosquamous carcinoma has recently been related to squamous-cell carcinoma. A strong association with HPV was found (25).

Distinction between cervical and endometrial adenocarcinoma

Determining the site of origin of an adenocarcinoma of the cervix may be difficult, particularly in curettage material. In particular, for endometrioid and endocervical types of adenocarcinomas immunohistochemistry may be useful in determining the site of origin. Endometrial adenocarcinomas usually express estrogen receptors (ER) and vimentin but lack CEA expression and usually do not contain HPV DNA. In contrast, endocervical adenocarcinomas are negative for ER and vimentin, show positivity for CEA, and contain HPV DNA. Therefore, a combination of ER, vimentin, and CEA can be applied to determine the site of origin (30). HPV in-situ hybridization can be used as an additional tool (31). The value of p16 immunohistochemistry has been challenged, in particular, because non-endometrioid adenocarcinomas of the endometrium, such as mucinous and serous carcinomas, frequently express p16, as do most endocervical adenocarcinomas. For serous and clear cell carcinomas, determining the site of origin can be very difficult.

Rare types of cervical carcinoma

Adenoid-basal carcinoma and neuroendocrine carcinoma are encountered within this group. These tumors are rare and thus of limited clinical significance. An association with HPV has been found for most types, although less frequently compared to squamous-cell carcinoma. No distinctive precursor lesions have been found for these tumors. Adenoid-basal carcinoma is slow-growing but lacks a clinically visible tumor (6). Metastases are rare.

Two types of neuroendocrine carcinomas of the uterine cervix are distinguished, small-cell carcinoma and large-cell neuroendocrine carcinoma, which are both rare and associated with poor prognosis (32, 33). Both express neuroendocrine markers, in particular NCAM (CD56) and synaptophysin, less frequently chromogranin A (34, 35). Other neuroendocrine peptides such as serotonin may be produced but do not cause endocrine symptoms. The Ki-67 labeling index is usually very high.

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