Condylomata of the uterine cervix and koilocytosis of cervical intraepithelial neoplasia

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SUMMARY In 202 women with koilocytotic atypia in cervical smears, 136 had predominantly small condylomata of the uterine cervix, and 66 had cervical intraepithelial neoplasia (CIN) of varying degree either with koilocytosis of the neoplasia or associated with condylomata. Koilocytosis correlated well with the histological diagnosis of condylomata, but occasionally it obscured the cytological evidence of CIN. Human papilloma virus particles were found in the cells of condylomata in 10 cases and in those of CIN II with koilocytosis in two cases of 21 examined ultrastructurally. There was evidence that the condyloma of the uterine cervix is a well-defined morphological entity and also that cytopathic changes similar to those seen in condylomata are present in some cases of CIN.

Condylomata acuminata are papillomatous lesions that arise mainly in the genital and anal regions of both sexes. The lesion is caused by a DNA tumour virus, the human papilloma virus (HPV), which forms the group of the papovaviruses with the polyoma viruses and the simian virus 40. The virus detected in condylomata acuminata^{1,2} has been defined as HPV 6 in a recent classification³ and differs biochemically⁴ and immunologically⁵ from that of the common wart. Studies on viral oncogenesis have shown that a wart has a unicellular origin, whereas condyloma acuminatum has a multicellular one.⁶ The multicellular derivation stresses the importance of environmental factors in the formative process of condyloma acuminatum, which is considered a transmissible venereal disease^{7,8} with a high incidence in populations who show sexual promiscuity.⁹ Condylomata acuminata occasionally undergo malignant transformation.¹⁰

In the uterine cervix condylomata acuminata are rare whereas less papillomatous and even flat lesions are more common. The latter have been considered possible early precursors of the exophytic lesions.¹¹ Their unsuspected frequency in asymptomatic women has been particularly stressed.¹² The cytological appearances in smears of early and florid condylomatous proliferations are similar. One of their most striking features is the cytoplasmic

clearing with nuclear atypia (koilocytotic atypia)¹³ which is now known to be a viral cytopathic effect.¹⁴ Ultrastructural investigations have shown the presence of papilloma virus particles in flat cervical condylomata,¹⁴ noncondylomatous warty lesions,¹⁵⁻¹⁷ koilocytotic cells,¹⁸ and exfoliated koilocytotic and dyskeratotic cells of flat condylomata of the uterine cervix.¹⁹ The similarity of condylomatous lesions to mild and moderate dysplasia of the uterine cervix and their possible association in some patients have been recognised.^{11,20-22} However, the problem of the possible significance of these viral lesions in the genesis of cervical carcinoma is still unsolved.

On the premise that koilocytotic cytopathic effects can be seen histologically not only in condylomata but also in some cases of cervical intraepithelial neoplasias (CIN),^{23,24} our study evaluated by histology and, in part, by electron microscopy the reliability of the cytological finding of koilocytotic atypia in both benign and CIN-derived cells in cervical smears and evaluates the possible significance of the association of condylomata and CIN and of the condyloma-like features occasionally displayed by CIN.

Material and methods

We examined 202 women aged between 17 and 66 years (mean 32.5 years, median 32) whose cervical

vaginal, endocervical smears (CVE) taken at the outpatient clinic of this institution contained koilocytotic cells or cells deriving from CIN with koilocytotic changes or both and whose biopsy material taken from the uterine cervix showed condylomata or CIN with koilocytosis, or both. Only four patients were postmenopausal. All patients underwent colposcopic examination and had directed biopsy specimens taken from their cervix within a month of the cytological diagnosis. Fifty-five patients with condylomata only had at least one repeat smear six months after biopsy.

The smears were stained with Papanicolaou's method. The biopsy material for light microscopy was fixed in Bouin's fluid, embedded in paraffin, and the 5 μ m-thick sections were stained with haematoxylin-eosin and PAS-haematoxylin with and without diastase pretreatment. The search for viral particles by electron microscopy was made in one vaginal and 21 cervical biopsy specimens. Of the former and of 15 cervical specimens, one-half were processed for electron microscopy. They were fixed for 2 hours at 4°C in 0.1 M phosphate-buffered 2.5% glutaraldehyde and after fragmentation, postfixed for 2 hours at 4°C in 0.1 M Millonig buffer containing 1% OsO₄, dehydrated through graded alcohols, and embedded in Epon. Suitable samples were selected under the light microscope from 1 μ m-thick sections stained with 1% methylene blue and 1% azure II. The tissue areas of interest selected on histological sections were removed from paraffin blocks of the remaining six cervical specimens, deparaffinised in xylene, and processed for electron microscopy after aldehyde fixation. Ultrathin sections of all biopsy specimens were collected on 150 mesh naked grids, double stained with uranyl acetate and lead citrate, and then examined with a Philips EM 300 electron microscope at 60 kV. Colposcopic examination was performed with a Zeiss colposcope before and after treatment with acetic acid and Lugol's solution.

In one case concomitant vulvar and in another vaginal condylomata acuminata were present, and biopsy specimens were taken. We examined the male partners of two patients at the same time and found penile condylomata acuminata which were biopsied.

Results

HISTOLOGY

In 136* cases (67.3%), biopsy material taken from the uterine cervix showed the presence of condylomata (group 1); in 39 (19.3%) there were condylomata and adjacent CIN (group 2), and in 27 cases (13.4%) CIN with koilocytosis of varying degree in the absence of condylomata was found (group 3).

*In one case with cervical condyloma a nonadjacent invasive squamous cell carcinoma (stage IB) was found.

Mean and median ages of the first group were respectively 32.2 and 31 years; mean and median ages of the second and third groups combined were respectively 33.7 and 32 years. The vast majority of the condylomata were small and flat or only moderately papillomatous. Fully developed condylomata acuminata were seen in only six cases. Occasionally, there was an association of the various types.

Group 1

In 104 out of the 136 (76.5%) cases with cervical condylomata, the histological picture was characterised by a honeycomb pattern of the epithelium with few cells in the superficial and intermediate layers. Cell size had increased, and a clear perinuclear halo not containing glycogen was present. The basal layer was well preserved. The nuclei of the cells with the halo were often eccentric and some of them were hypochromatic showing a "dusty" appearance while others were hyperchromatic and pyknotic. The nuclei were occasionally multiple. The mitotic index was low and no abnormal mitotic figures were found. The degree of acanthosis and hyperkeratosis of the epithelium and the amount of small cell infiltration of the underlying stroma were variable but usually mild to moderate. This appearance is defined as condyloma type 1 (Fig. 1a).

In the other 32 cases (23.5%) the changes were more severe. The majority of the cells had a very large cytoplasm, which was almost completely replaced by the koilocytic halo. The honeycomb pattern covered the whole thickness of the epithelium, with disorder of the stratification. The nuclei were hyperchromatic and often bizarre; multinucleation was common, as was karyorrhexis. In the intermediate layer there was occasional single cell keratinisation. Within the epithelium inflammatory cells were present. The mitotic index was also low in this lesion, and no abnormal mitotic figures were found. The more severe lesion described is defined as condyloma type 2 (Fig. 2a). An attempt to differentiate type 2 condylomata from CIN I or mild dysplasia with koilocytosis was unsuccessful.

Group 2

In 39 (19.3%) cases, single or multiple condylomata type 1 and 2 as described above were found adjacent to foci of CIN. In addition, a variable number of cells of the neoplastic lesions showed koilocytosis (Figs 3a and b). CIN II was associated with condyloma type 1 in 12 cases and with condyloma type 2 in six cases, and CIN III, respectively, in 15 and six cases.

Fig. 1a *Flat condyloma of the uterine cervix type 1. Haematoxylin and eosin $\times 100$*
 Fig. 1b *Cytology of flat condyloma type 1. Papanicolaou $\times 400$*

Fig. 2a *Flat condyloma of the uterine cervix type 2. Haematoxylin and eosin $\times 100$*
 Fig. 2b *The cytology of flat condyloma type 2. Papanicolaou $\times 250$*

Group 3

Of the 27 cases (13.4%) with CIN with koilocytosis and no condyloma, 12 were rated as CIN II (Fig. 4a) and 15 as CIN III (Figs 5a and b). The cytopathic changes such as perinuclear clear halos, abnormal pyknotic nuclei, multinucleation, and single cell keratinisation were variable in frequency and predominantly evident in the most superficial layers of

the neoplastic epithelium (surface koilocytosis). In some cases hyperkeratosis was present.

The total number of cases of CIN irrespective of the association with condylomata was therefore 66: 30 of CIN II and 36 of CIN III. The data are summarised in Table 1. The histology of the vaginal, vulvar, and penile condylomata acuminata was consistent with the clinical diagnosis.

3a

3b

3c

Fig. 3a Flat condyloma type 1 (right end of the epithelium) and transition to initial CIN with koilocytosis (left end). Haematoxylin and eosin $\times 100$

Fig. 3b Enlarged area of A: maturation arrest and abnormalities of the nuclei in the deep layers of the epithelium. Haematoxylin and eosin $\times 250$

Fig. 3c Cytological appearance of CIN II with koilocytosis: perinuclear halos are present. Papanicolaou $\times 400$

4a

4b

Fig. 4a CIN II with koilocytosis. The maturation arrest with nuclear abnormalities involves predominantly the lower and the intermediate layers, whereas cytopathic changes are recognisable in the superficial layers of the epithelium. Haematoxylin and eosin $\times 250$

Fig. 4b Cytological appearance of CIN II: the cytoplasm in part is fairly large and pleomorphic and contains small halos. The nuclei are atypical, bizarrely shaped and often multiple. Papanicolaou $\times 400$

5a

5b

5c

Fig. 5a CIN III with marked koilocytosis and a high mitotic index. Haematoxylin and eosin $\times 250$

Fig. 5b CIN III with moderate koilocytosis and hyperkeratosis. Haematoxylin and eosin $\times 250$

Fig. 5c Cytological appearance of CIN III. The cells show marked nuclear atypia. Perinuclear halos are very rare and small. Papanicolaou $\times 250$

Table 1 Cervical condylomata types 1 and 2 and their association with CIN in relationship to the presence of koilocytosis in cervical smears from 202 patients

	Condyloma*	CIN II	CIN III	Total
Condyloma type 1	104	12†	15†	131
Condyloma type 2	32	6†	6†	44
Absence of condylomata‡	—	12	15	27
Koilocytosis in cytology	136	30	36	202

*Group 1 cases with cervical condylomata only (n = 136).

†Group 2 cases of CIN associated with condylomata (n = 39).

‡Group 3 cases of CIN with koilocytosis (n = 27).

CYTOLOGY

The cytological features of the CVE smears of the 136 cases with histologically proven condyloma were characterised by the presence of sheets of cells with various degrees of dyskeratosis and sheets or cohesive clusters of superficial and intermediate cells with large cytoplasm and a perinuclear clear halo

(koilocytotic atypia) (Fig. 1b). The nuclei were often eccentric, occasionally enlarged, with pale dusty chromatin, and resembled those described as condylomatous intermediate cells²⁰ but were more often hyperchromatic and pyknotic. The cytoplasm was usually markedly polychromatic, whereas single cell cytoplasmic keratinisation and phagocytosis of granulocytes were rare. Multinucleated cells were quite numerous in some cases, and their overlapping and hyperchromatic nuclei showed a blackberry-shaped pattern. In general, a large number of multinucleated cells, isolated keratinised cells, and phagocytosis of granulocytes were related to the cases with condyloma type 2 (Fig. 2b). The cytological follow-up of 55 cases with both condylomata type 1 and 2 showed no koilocytotic cells in smears of 60% of the women after six months, while they persisted unchanged in 40%.

The cytological findings of the 66 cases in which the histology showed either CIN with koilocytosis or the combined presence of condylomata and CIN

were similar (Figs 3c, 4b, 5c). In general, neoplastic cells with the characteristic perinuclear halo were rare. They were more common in CIN II than in CIN III. In the smears from cases with CIN III with koilocytosis, the atypical cells were predominantly single and roundish with little cytoplasm. However, some of them had a moderately large pleomorphic cytoplasm which was either acidophilic or almost unstained. The atypical nuclei were hyperchromatic, pyknotic, bizarrely shaped, often multiple, and often associated with retrogressive changes. Perinuclear halos were small and rare. A variable number of neoplastic cells without koilocytosis and of non-malignant koilocytes was also found.

CYTOHISTOLOGICAL CORRELATION (Table 2)
The cytological diagnosis in 125 of the 136 cases of cervical condylomata (group 1) had been simply koilocytosis, whereas in the remaining 11 cases the diagnosis of CIN II with koilocytosis was subsequently revised and downgraded. The histological pattern of five of these 11 cases was consistent with condyloma type 2. The cytohistological correlation of the 66 cases of either CIN with koilocytosis or CIN with accompanying condylomata showed that in 18 the cytological diagnoses had not reflected the actual degree of severity of the lesion. However, the revision reconfirmed the original underestimated cytological diagnoses in five cases of CIN II and nine of CIN III, whereas in four cases of CIN III the smears were reclassified as inadequate.

Table 2 *Cytohistological correlation*

Cytology	Histology			Total
	Condyloma	CIN II + K $\pm$ C	CIN III + K $\pm$ C	
Koilocytosis	125 (92%)	5	4*	134
CIN II + K	11	25 (83%)	9	45
CIN III + K	—	—	23 (64%)	23
Total	136	30	36	202

K = koilocytosis; C = condyloma.

*Superficial smears.

COLPOSCOPY AND COLPOSCOPIC-HISTOLOGICAL CORRELATION

Three main colposcopic patterns were seen in 81 of 136 cases (59%) with histologically proven condylomata. In 38 cases we found leukoplakia-like condylomatosis made up of sharply defined areas of different shapes and sizes, whitish-ground glass in colour, and slightly raised above the mucosa of the portio with either straight or branching vessels. In 37 cases we found white-patches condylomatosis showing multiple, small, roundish, smooth, and whitish formations which were slightly raised above

the ectocervical mucosa and surrounded by a thickening at the periphery. In the remaining six cases we found florid condylomatosis revealing a multicentric, whitish, elevated proliferation on the ectocervix with a rough "cobblestone"-like surface, which was poorly vascularised and did not show atypical vessels. In no case of condyloma was there colposcopic evidence of atypical transformation.

In the 18 cases of CIN II associated with condylomata, the latter were recognised colposcopically in 17, of which 10 showed a leukoplakia-like pattern and seven white patches. In the 21 cases with CIN III with condylomata, colposcopy showed mixed patterns in seven.

ELECTRON MICROSCOPIC FINDINGS

Spherical viral particles, approximately 350 to 400 Å in diameter and morphologically identical to human papilloma virus (Figs 6, 7), were found in 12 (57%) of the 21 cervical lesions examined. Ten of the positive lesions had been identified on semithin sections as condylomata. In two of these cases the histology of the whole biopsy material had shown CIN III adjacent to the condyloma. In the other two cervical lesions with viral particles, semithin sections showed CIN II with koilocytosis. Of the nine cervical lesions that exhibited no viral particles, seven were condylomata and two CIN III with koilocytosis.

Fig. 6 *Intranuclear viral particles grouped around chromatin clumps or independent in the nucleoplasm. $\times 61\,000$*

Fig. 7 A higher magnification of intranuclear viral particles showing a dense core with a surrounding clear halo. Note their regular form and size. $\times 177\,000$

The viral particles were contained in the nuclei of superficial epithelial cells. Most particles were single and either freely scattered throughout the nucleoplasm or closely associated with chromatin clumps. Others were assembled in small or large clusters in the nucleoplasm. Viral particles of the cytoplasm were found in cells with a ruptured nuclear envelope (Fig. 8). In six cases of condylomata and in one of CIN II with koilocytosis, a small number of viral particles was present in a few nuclei, whereas in four

condylomata cases and in the other case of CIN II with koilocytosis there were many nuclei with viral particles and most of them had a high concentration of viral particles.

In the cells of both condylomata and CIN II with koilocytosis, two types of nuclei with viral particles were observed. Many were enlarged, had irregular profiles and a clear aspect, contained large clumps of chromatin mainly attached to the nuclear envelope, and showed no separation between the nuclear envelope and clumped chromatin (Fig. 9a and b). Others with a round shape and a markedly diminished size were striking because of the compact arrangement of their chromatin clumps. The margins of the chromatin were prominent and the nuclear envelope unidentifiable (Fig. 10a and b). The nuclei were surrounded by a large clear area almost devoid of cytoplasmic organelles. In this area a few cytoplasmic remnants were recognisable, and they were scattered sparsely or sometimes condensed and aligned on the outer margin of the nuclei. Occasionally glycogen-like material such as rare isolated granules was observed. The clear perinuclear area was delineated at the periphery by a dense narrow band of cytoplasm containing irregularly arranged bundles of tonofilaments. The boundary between the perinuclear and outer area of the cytoplasm was sharply defined.

Numerous papilloma virus particles were also observed in the vaginal condyloma acuminatum examined. They were dispersed or arranged in a paracrystalline fashion in the enlarged nuclei of the superficial epithelial cells, which showed dense peripheral and clear perinuclear areas of cytoplasm as described above.

Fig. 8 Part of a nucleus showing the ruptured nuclear envelope (arrows). Single viral particles can be seen in the cytoplasm. $\times 28\,000$

Fig. 9a Benign koilocytes with large nuclei: the morphology of the nuclei in semithin section. Methylene blue-azure II $\times 1000$

Fig. 9b A large nucleus with irregular outline showing a thin margin of the clumped chromatin. A cluster of viral particles independent of chromatin can be seen in the nucleoplasm. $\times 14\,000$

Fig. 10a Small nuclei in a semithin section: prominent margin of the chromatin. Methylene blue-azure II $\times 1000$

Fig. 10b A small, round nucleus with large compact clumps of chromatin. Note the nucleoplasm entirely filled with viral particles. $\times 16\,000$

Discussion

The results show that the cytological diagnosis of koilocytosis without marked nuclear abnormalities in CVE smears was, on the whole, reliable with reference to the presence of condylomata of the cervix. However, it is recognised that the reverse may not be true.²⁵ The occasional overestimation of the cytological diagnosis and its interpretation as CIN II was probably related to the traditional cytological approach.¹¹ However, since in about half of the overestimated cases histology showed a condyloma type 2, which more closely resembles CIN than does type 1, the low grading after revision was limited to less than 5% of the cases. We did not observe marked nuclear atypia indicative of a malignancy such as that described for condylomata acuminata.²⁵ On the contrary, there was underestimation of the cytological diagnosis of CIN when koilocytosis was a prominent feature. The decreased accuracy of cytology in some of these cases may be related to the peculiar histological structure of the lesions, with well-preserved neoplastic cells of diagnostic value located in the deeper layers and koilocytotic cells not readily recognised as being neoplastic being found superficially. The smears taken from some of the cases of CIN with koilocytosis, and particularly from those with hyperkeratosis, showed the presence of parakeratotic cells and abnormal, pleomorphic cells but which appeared mature with a large cytoplasm. The resulting pattern corresponded in part to those described as pleomorphic parakeratosis and pleomorphic keratinising dysplasia.²⁶

Although the follow-up was short and incomplete, it seems that the cytological changes of condylomata disappear at least temporarily in a high percentage of the cases.^{12 15 20 27} In view of the fact that condylomata type 1 and particularly type 2 may be interpreted histologically as mild or moderate dysplasia and koilocytosis in smears as mild dysplasia, the reported high regression rate of these lesions finds a partial explanation. Because there is frequent spontaneous regression and because their natural history is uncertain, small condylomata of the cervix should not be overtreated but kept under clinical and cytological control. The incidental finding of penile condylomata acuminata in the sexual partners of two patients stresses the indication for the systematic examination of the couple.^{28 29} The colposcopic findings were consistent with the histological report in about 60% of the cases with condylomata and were essentially the same in the cases with condylomata and CIN. In most of the cases of CIN with or without condylomata, the colposcopic picture was, however, dominated by the

areas of atypical transformation from which the biopsies were taken. Therefore, the absence of accompanying condyloma in some cases of CIN with koilocytosis may have been a sampling error.

In keeping with the rarity of papillomatous condylomata of the cervix, the colposcopic pattern of florid condylomatosis was the least common. The leukoplakia-like pattern had to be distinguished from the true mosaic on the basis of the appearance of the vessels, whereas the white-patches condylomatosis had to be differentiated from cornified glandular outlets. The latter was the most difficult type to recognise at colposcopy, and for its identification the preceding cytological diagnosis of koilocytosis was very helpful.

The presence of intranuclear viral particles in 12 of 21 cases examined expands our own results on four of the present cases¹⁴ and confirms those published by others.¹⁵⁻¹⁹ Frequently, as in condylomata acuminata, a few viral particles and only a small number of koilocytes were present. The viral particles detected could not be distinguished by their number, ultrastructure and intranuclear distribution from those that have been identified in condylomata acuminata and considered to be their aetiological agent.² The similarity with the findings in condylomata acuminata suggests that the cervical infection by a papilloma virus is responsible for the cytopathic changes of condylomata non-acuminata as well as of CIN. In accordance with the histological findings, the clear perinuclear halos of the koilocytes did not contain glycogen and they may be related to oedema and vacuolisation of the cytoplasm.³⁰

It is noteworthy that in published reports in the examples given of the histological appearance of the various grades of CIN, often in the superficial and occasionally in the deeper layers of the epithelium, there are cells with evident koilocytosis.^{31 32} Our histological findings clearly indicate that the small and predominantly flat condyloma of the uterine cervix, also named noncondylomatous wart virus infection,¹⁷ is a well-defined entity even though it may show some variations in appearance. The degree of atypia shown by type 2 is compatible with cytopathic effects and is not necessarily neoplastic in origin. Cellular pleomorphism does not allow any clear distinction from CIN. Also we cannot say whether CIN II and III with koilocytosis are just CIN with superimposed viral infection or peculiar precursors of cervical carcinoma. It should be noted that all our cases of CIN III with koilocytosis were of the large cell type and never of the small cell type.

The ultrastructural findings of papilloma virus particles in CIN II-derived cells as in the present series and in cells originating in areas surrounding carcinoma *in situ*¹⁷ and from a cervix with infiltrating

carcinoma¹⁴ do not support any causal relationship between papilloma virus infection and cervical neoplasia. The same applies to the coexistence of condylomata and CIN and to the apparent transition from the first to the latter. Undoubtedly, the cases of proven progression of "verrucous dysplasia" to CIN³³ and those of development of mild dysplastic lesions with koilocytic atypia after cone biopsy for CIN III²⁷ point to an interaction of papilloma virus infection of the human uterine cervix with the pre-malignant and malignant transformation of the cells. Should this be confirmed, then the hypothesis, proposing the existence of several pathways, both infectious³⁴ and noninfectious,³⁵ leading to cervical carcinoma, would gain ground.

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