PREMALIGNANT EPITHELIAL CHANGES IN THE UTERINE CERVIX OF WOMEN AGED LESS THAN THIRTY WITH SPECIAL EMPHASIS ON THE COEXISTENT CONDYLOMATOUS LESIONS

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Summary

One hundred and sixty two women aged less than 30 with either a dysplastic change or carcinoma in situ of the squamous epithelium of the uterine cervix were histologically assessed with special emphasis on the detection of the recently described condylomatous lesions (the flat, inverted and the papillomatous ones) caused by human papilloma virus (HPV).

A total of 134 condylomatous (CO) lesions were discovered, the flat type being the most frequent one (75.4%) followed in decreasing order of frequency by the inverted (14.2%) and the papillomatous condylomas (10.4%). The classical papillomatous condylomas were characteristically associated with mild dysplasias, while the flat and inverted ones were more common in cases of the more severe epithelial atypias. All the patients under 20 showed CO changes associated with their atypias, which was interpreted to indicate that the coexistent condyloma infection accelerates the development of these lesions. The clinical behavior of the epithelial atypias studied was consonant with that of cervical dysplasias in general in the sense that the severity of the atypia increased with the advancing age of the patients.

The possible role of HPV, the etiologic agent of the condylomas, in the development of uterine cervical carcinoma was discussed in the light of the present observations, and the conclusion was drawn that this might be the agent responsible for or contributing to the evolvement of this cancer.

Genital warts (Condylomata acuminata) are known as venereally transmitted lesions of the squamous epithelium previously considered as entirely benign tumors caused by human papilloma virus (HPV) [1-15]. The structure and immunological properties of HPV have been subjected to considerable number of studies during the recent few years when an infectious agent as a possible cause of cervical carcinoma has been searched for [1-35].

Support to the concept that HPV could be involved in human squamous cell carcinogenesis has been provided by the establishment of the three different histological manifestations of the condylomatous lesions (the flat, inverted and the papillomatous ones) [5,6,31,32,36,37], by the increasing number of reports on the observed malignant

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transformation of the genital wart [4,11,13,16,18,23,24,25,26,29], by the observations on their frequent intimate association with epithelial dysplasias [4,5,6,13,31,32,36-41] and even with invasive squamous cell carcinomas of the uterine cervix [39-44] and of the bronchus [45-47].

During the recent years, premalignant and malignant changes in the uterine cervix of teenagers have been reported with increasing frequency [48-50], and because the peak incidence of the condylomatous lesions and HPV-antibodies are encountered in women less than thirty [5,14,15,20,31,32,36], it seemed feasible to undertake a study of the possible relationship between these two diseases (condylomas and epithelial premalignant lesions) in these young women.

Material and Methods

The present series consists of 162 women aged less than thirty, and who had a histologically verified dysplastic or neoplastic epithelial lesion in their uterine cervix. All patients had been admitted to hospital due to an abnormal finding in their routine cervical smear, and all of them were subjected to either colposcopy or conization depending on the severity of the cervical lesion concerned. The cervical specimens obtained by either of these methods were collected for study from the files of the Departments of Pathology, Jorvi Hospital, Espoo, Päijät-Häme Central Hospital, Lahti, and Kuopio University Central Hospital, Kuopio, Finland. All the specimens had been routinely processed into 4-micron histological sections, and stained with hematoxylin-eosin or van Gieson stains.

A re-evaluation was instituted for all the specimens with regard to the degree of the epithelial atypia. Each lesion was classified into one of the following five categories: Degree I, mild dysplasia; Degree II, moderate dysplasia; Degree III, severe dysplasia; Degree IV, carcinoma in situ; and Degree V, an invasive carcinoma of the uterine cervix.

The morphological details of the three different condyloma types (the flat, inverted and the papillomatous ones) are to be found in a number of previous publications [5,31,32,36,37,39,40,41,43,44,46,47], and will not be repeated in the present text. (Figs. 3-6).

For the statistical calculations, chi-square test and Student's t-test were applied, where indicated.

Epithelial lesion with (CO) and without (N-CO) the coexistent condylomatous changes in the different age groups studied are depicted in Fig. 1. In women less than 20, epithelial atypias were always accompanied by the CO lesions, which far outnumbered the N-CO lesions in the whole series ($P < 0.001$).

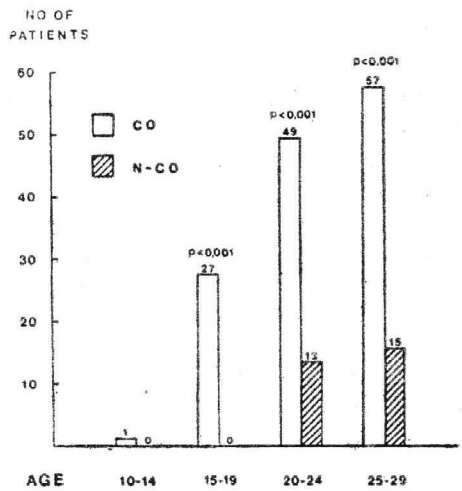

Fig. 1

The age distribution curve of the condylomatous lesions is shown in Fig. 2. An elevation into a relatively steady level is observed in women beyond 18 years of age, whereafter the peak frequency in the present patients is found in women aged 29.

TABLE 1

Epithelial atypia related to the age of the patients

Age Groups	Degree of Epithelial atypia									
	I		II		III		IV		V	
	No.	%	No.	%	No.	%	No.	%	No.	%
10—14	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0
15—19	14	51.9	4	14.8	7	25.9	2	7.4	0	0.0
20—24	28	45.2	15	24.2	10	16.1	8	12.9	1	1.6
25—29	24	33.3	12	16.7	20	27.8	16	22.2	0	0.0

TABLE 2

The different condyloma types related to the age of the patients

Age groups	Flat condyloma		Inverted condyloma		Papillomatous condyloma	
	No.	%	No.	%	No.	%
10—14	0	0.0	0	0.0	1	100.0
15—19	23	85.2	3	11.1	1	3.7
20—24	36	75.0	7	14.5	5	10.4
25—29	42	72.4	9	15.5	7	12.1

The relationship between the age of the women and the degree of epithelial atypia is summarized in Table 1. The frequency of the more severe atypias seems to increase with the advancing age, as commonly accepted.

The different condyloma types related to the age of the patients are depicted in Table 2. The flat type seems to be the most frequent condyloma in all age groups except in that of the youngest patients (below 15), where the one case observed was a papillomatous one. (Fig. 3.)

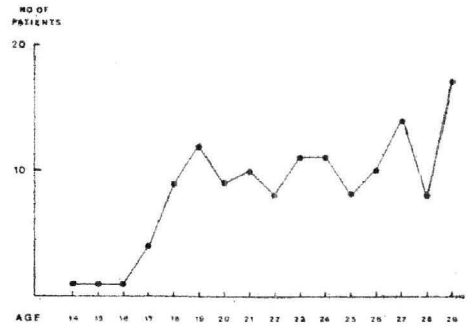

Fig. 2

Table 3 shows the relationship between the different condyloma types and the degree of epithelial atypia. The histological and cytological changes of a flat condyloma are shown in (Figs.4&6). The classical papillomatous type seems to be typically associated

TABLE 3

The different condyloma types related to the degree of epithelial atypia

Type of condyloma	I		II		III		IV		V		Total series	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Flat	36	35.6	22	21.8	27	26.8	16	15.8	0	0.0	101	75.4
Inverted	4	21.0	5	26.4	4	21.0	6	31.6	0	0.0	19	14.2
Papillomatous	10	71.4	2	14.3	2	14.3	0	0.0	0	0.0	14	10.4
Total series	50	37.4	29	21.6	33	24.6	22	16.4	0	0.0	134	100.0

Fig. 3 A general view on a classical genital wart, the papillomatous condyloma of the uterine cervix. The lesion is characterized by papillomatosis, acanthosis, elongation and thickening of the rete pegs, parakeratosis and cytoplasmic vacuolization (koilocytosis). (H and E, original magnification × 25).

with mild and moderate dysplasia, while the inverted one is most frequently encountered in cases of the in situ carcinomas. (Fig. 5).

Discussion

The viral etiology of human genital wart seems to be beyond doubt[1-15,16-35]. Viral particles closely resembling those found in genital warts were recently discovered in cutaneous lesions (epidermodysplasia verrcuiformis) related to genital warts[21,23], as well as in the cells of the uterine cervical lesions classifiable as flat condylomas[2,5,6,32, 38,51]. These recent findings support the idea postulated by Meisels et al[5], [31,32] that these newly discovered epithelial lesions called flat and inverted condylomas are caused by HPV, and, indeed, can be considered as condylomatous in origin like the classical papillomatous genital warts[13].

There are ample documented cases where invasive squamous cell carcinoma has been shown evolving from a preexisting genital wart[4,11, 13,16,18,23-26,29]. The attempts to disclose the viral particles in these lesions after the malignant change has taken place, have not been successful, however[18,21,23,26,52]. As recently pointed out[29], this does not in itself rule out the possibility that HPV could play a role in human squamous cell carcinogenesis. On the contrary, this failure to detect viral particles in these malignant lesions in man seems to be in agreement with the observations made in the animal models of the papillomatous tumors (Shope rabbit papilloma), in which the malignant transformation is succeeded by the disappearance of the viral particles[29,53,54]. The failure to find the viral particles in these lesions most probably is due to the fact that viral DNA is incorporated in the cellular genome thus escaping the detection by electron microscopy[18].

It is accepted that the condylomatous lesions are venereally transmitted and most frequently encountered in young women living in sexual promiscuity[5,8, 9,10,14,15,36]. There are authors ready to admit that cervical carcinoma, too, is primarily transmitted by sexual contact [5,12,29,30,33,34,35], thus raising the question about the possible causal relationship between these two diseases[10,14,15],

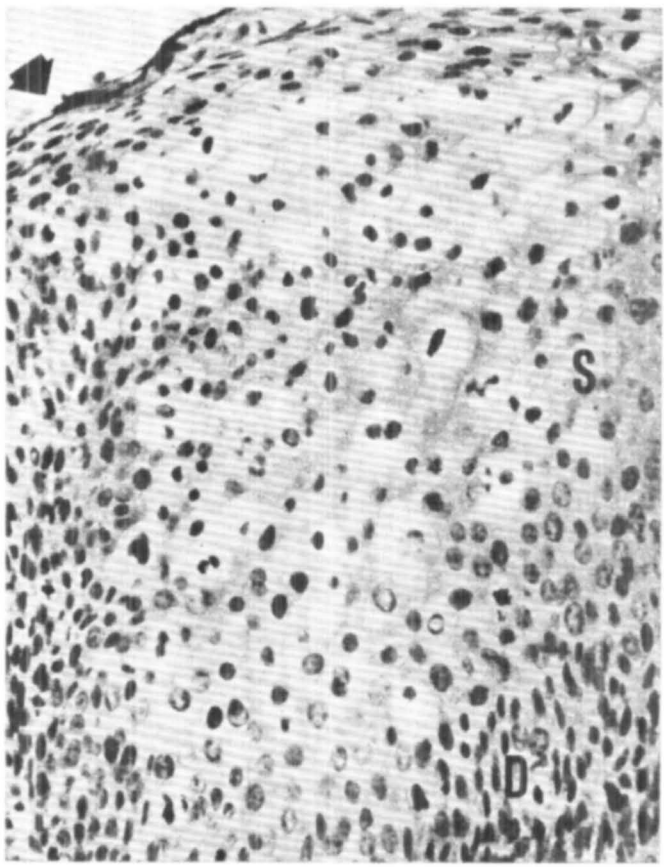

Fig. 4 A medium power detail of an epithelial lesion classifiable as flat condyloma. The lowermost dense layers (D) are composed of basaloid cells, and are not markedly altered. Towards the surface, distinct koilocytes are hyperchromatic, frequently pyknotic, and irregular in size and shape. Binucleated cells are common. All the nuclei are surrounded by a clear halo consisting the bulk of the cytoplasmic volume. The epithelium is covered by a layer of dyskeratotic superficial cells (arrow).
(H and E, original magnification × 250).

and malignant changes of the uterine cervix in teenagers[48-50]. In a series of studies[39-42, 44], both histological and cytological evidence for the presence of condylomatous changes in the uterine cervix closely associated with the dysplastic and neoplastic lesions has been recently obtained. The present study was specially focussed on the youngest age groups of women for the reasons discussed above. Special emphasis was placed on the detection of the three condyloma types in the cervical epithelium harboring a dysplastic or in situ carcinomatous lesion.

The results indicate that epithelial lesions fulfilling the recently outlined criteria of the condylomatous changes [5,31,32,36,37,39,40,41,43,44,46,47], were found in 134 cases (82.7 per cent). This is a considerably higher figure than that obtained in a series of women covering all age groups[40,41]. This is due to the fact that the mean age of the women with CO lesions was observed to be almost ten years less than that of women with N-CO lesions[39-41]. This has been interpreted to suggest that the presence of CO accelerates the development of epithelial dysplasia/neoplasia which requires more time to develop in the absence of CO

[32,43]. Of special interest in this respect is a recent report of an increased incidence of cervical carcinomas in wives of penile cancer patients[28] substantiating a hypothesis on the role of the high-risk male in the etiology of cervical carcinoma[35]. The presence of a sexually transmitted infectious agent would also explain the reported increase in the incidence of premalignant

lesions[41]. The present results are consistent with this view (Fig. 1) by indicating that none of the patients under 20 years of age had developed epithelial atypia without the coexistent CO lesion. The age distribution curve of the condylomatous lesions in the present series (Fig. 2) coincides with that of the genital warts in general (5) thus substantiating the concept that the flat and the inverted lesions are also of viral (HPV) origin[5,31,32,43]. Further support to this idea is provided by the studies of the prevalence of HPV-antibodies[20], with the frequency peaks paralleling those of the CO lesions in the present series.

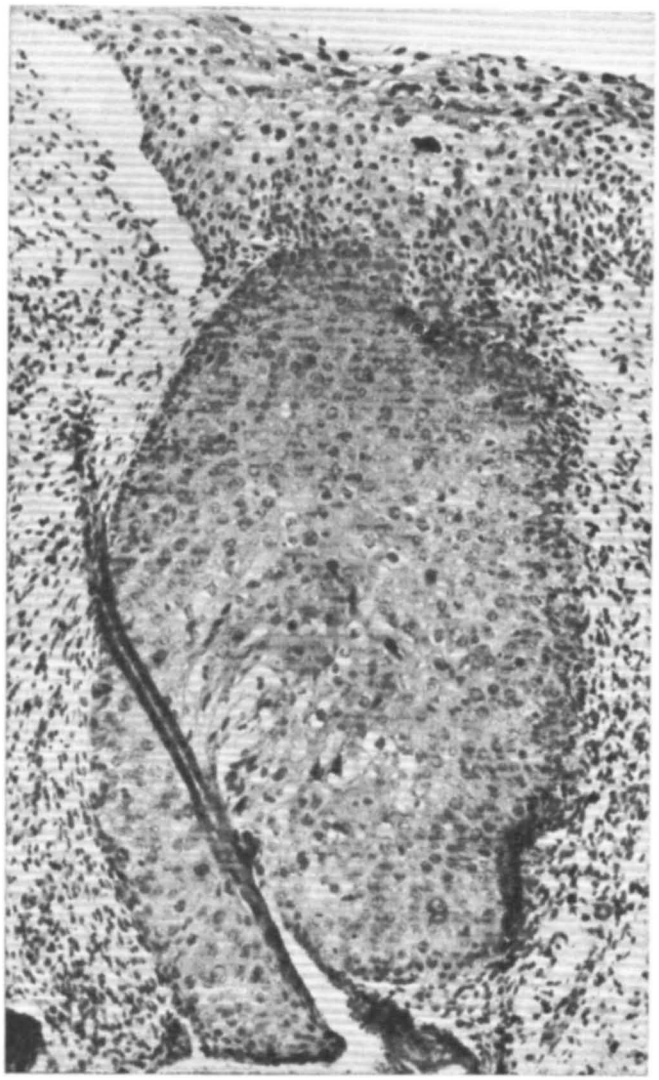

Fig. 5 A characteristic presentation of an inverted "endophytic" condyloma. The epithelium is characterized by the morphological alterations depicted in Fig. 4 for the flat type condyloma. In addition, the lesion is characterized by endophytic proliferation resembling an inverted papilloma with pseudoinvasive penetration into the underlying glandular openings. (H and E, original magnification × 100).

When the different degrees of epithelial atypia are correlated with age of the women in the present series (Table 1), a steady progress from mild dysplasias into the more severe atypias is evident with the advancing age. This is consistent with the general behaviour of the cervical dysplasias, and indicates that very few if any of the dysplasias associated with the condylomatous changes are reversible[43]. An attempt was made to correlate the three condyloma types with the age of the patients (Table 2), but no clearcut association between these two parametres could be found. In a previous study[41], papillomatous condyloma was found to be characteristically the lesion of the youngest age groups (women below 30), but as evidenced by the figures in Table 2, no direct correlation to the age was found

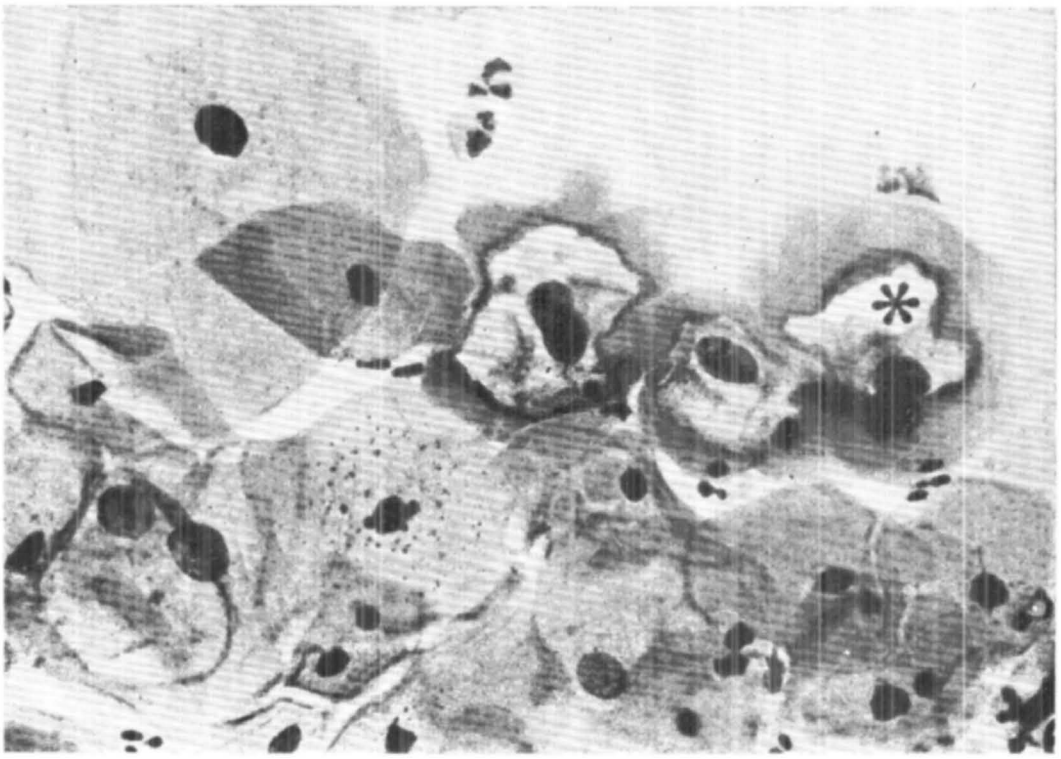

Fig. 6 A typical cervical smear derived from a condylomatous epithelial lesion. Characteristic koilocytes (asterisk) are depicted showing all the features described in Fig. 4. The pyknotic nuclei are surrounded by a clear halo making up the bulk of the cytoplasm. One of these cells is clearly binucleated.

(Papanicolaou stain, original magnification × 400).

within the different age groups in the present study. When related to the degree of epithelial atypia (Table 3), the papillomatous type is most common in cases of mild and moderate dysplasias, while the other two are more frequent in cases of the more severe atypias. This is consistent with previous observations[39-41], and explains why severe atypias were infrequently found in the series of the classical genital warts[13]. Most of these more severe atypias seem to be associated with the recently described flat and inverted condylomas (Table 3).

The present study indicates that condylomatous lesions are extremely common findings in the dysplastic and even in the neoplastic epithelium of the uterine cervix in young women. These results are in agreement with the previously presented data that CO lesions are sexually transmitted and common in young women living in sexual promiscuity[5,8,9,10,14,15,36], although this last mentioned fact was not surveyed in the present work. The author is tempted to suggest that much of the reported increase in the frequency of premalignant epithelial changes in the uterine cervix of teenagers[48-50] is most probably attributable to an infectious agent, HPV being the primary candidate of suspicion. In the light of the present observations, the possibility should be borne in mind that HPV might be the agent responsible for or contributing to the development of uterine

cervical carcinoma. The detection and the proper treatment of these lesions seems to require the focusing of the gynecological mass-screening programs on these younger age groups, too.

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TRUE or FALSE

Study of epidermal cells by amniocentesis can provide evidence for questions of paternity.

(See Page No. 130)