Condylomatous tumours of vulva, vagina, and penis

Relation between histological appearance and age

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SUMMARY Among 237 cases of condyloma diagnosed in Uganda between 1964 and 1975 seven types of lesions were defined. Three of these were found within a wide age range in both young and elderly people, namely, the common (49.4%) and the flat (2.0%) condyloma acuminatum, and condyloma acuminatum of irregular outline (13.5%). Four variants, on the other hand, fell into different age groups. Condyloma acuminatum, showing marked cell death (5.1%) and observed exclusively among girls in the first decade of life, displayed numerous acidophil bodies, presumably reflecting single cell necroses. Condylomata acuminata showing marked acanthosis (16.9%) were found in patients between 12 and 30 years, dysplastic condylomata acuminata (5.9%) between 20 and 62 years, and proliferative (giant) condylomata acuminata (7.2%) between 31 and 80 years of age. In the latter two groups of lesions, the inflammatory stromal infiltrate was more prominent, but cytoplasmic vacuolation, often believed to be a sign of viral infection, was seen less frequently than in the remaining types. In young people, the features seen resemble, therefore, a cytotoxic and/or vacuolating viral infection, whereas the dysplastic and proliferative changes observed in older patients are compatible with malignant transformation being under way.

The terminology and classification of papillary squamous tumours occurring on the genitalia are at variance. According to the macroscopic appearance, early reports distinguish the common, the flat, and the giant condylomata acuminata, and these terms are still in use today.^{1 2} Later subdivisions distinguish condylomata acuminata of young people showing cytoplasmic vacuolation in the upper epithelial layers from squamous cell papillomas of the elderly, in which precancerous changes are seen but only little vacuolation.^{3 4} By contrast, according to a recent authoritative recommendation, the only difference between a squamous cell papilloma and a condyloma acuminatum is that the former is a solitary and the latter a multiple lesion.⁵

Many examples of papillary squamous tumours have been observed which were neither benign nor fully malignant. For such lesions, the terms giant condyloma acuminatum, carcinoma-like condyloma, and condyloma-like carcinoma were suggested.¹ Furthermore, the term verrucous carcinoma was

introduced, embracing all these kinds of tumours,⁶ or referring only to giant condylomata acuminata showing malignant change in the form of true invasion.⁷ However, another proposition is to retain the term verrucous carcinoma only for cases that show invasion by large epithelial islands conforming to a solid growth pattern⁸ and to describe in full detail whatever combinations are seen within a single tumour.⁹

When analysing their age distribution in biopsy series of cases, two groups of condyloma acuminatum were found which occurred mainly in young and less often in elderly persons and thus preceded the cases of carcinoma by decades and years, respectively, suggesting perhaps that these lesions are precancerous. They showed a low risk and long time interval to subsequent carcinoma in young patients and a high risk and short time interval in older patients.¹⁰⁻¹² It seemed likely that there were variations not only in age distribution but also in histological appearance, and it was decided, therefore, to reassess the cases from Uganda where most material had been collected.

Material and methods

Slides of all cases diagnosed in the Pathology Department of Makerere University in Kampala between 1964 and 1975 were taken out from the files. This department harbours the only histopathology service for all of Uganda, a country with approximately 12 million inhabitants and a high incidence of cancer of the penis.¹³ A case was defined as a lesion reported as condyloma acuminatum, venereal or genital warts, or squamous cell papilloma. The tumours had occurred mainly on the vulva, vagina, and penis, but a few examples in which the origin was the orifice of the urethra were also included because it was felt that other such cases could have been reported simply as arising from a genital site. Slides could not be obtained in 20.9% and 7.6% of female and male cases respectively.

Histological examination was done without knowledge of the sex or age of the patient or the site of the lesion. A number of features were assessed, namely, the degree of cytoplasmic vacuolation of the epithelium, the density of stromal inflammatory infiltration, dysplastic changes, and the portion of epithelial and fibrovascular tissue seen in the condylomatous tumour. Nine cases which fell outside the histological range of condylomata acuminata were excluded from the analyses. These showed borderline changes either to malignancy or to hyperplastic lesions. Cytoplasmic vacuolation is considered to be a normal occurrence on all mucosal surfaces, but a distinction from vacuolation seen in condylomata acuminata was not attempted; the changes were difficult to distinguish, particularly

when of negligible degree. The cases of carcinoma were taken from the Kampala Cancer Registry which uses the biopsy service for case finding (Table 2).

Results

Seven variants of condylomatous tumours could be distinguished histologically and were divided into the following two groups (Tables 1 and 2).

WITHIN A WIDE AGE RANGE

Common condylomata acuminata, the most frequently seen type of lesion, were encountered mainly in patients between 10 and 30 years old and less often in the 0-9 and 30-50 year age groups (Fig. 1). These cases showed elongated, acanthotically enlarged rete ridges, together with increased formation of fibrovascular papillae, and resembled closely the less frequently observed irregular condyloma acuminatum (Fig. 2). The distinguishing features were that these latter lesions seem to occur in slightly older age groups among men (Table 2) and have an outline of rete ridges showing notched and less broad epithelial processes. The few cases of flat condylomata acuminata were characterised by a broad base and formation of fibrovascular cores towards the surface; they occurred in patients aged 19-40 years (Fig. 3).

IN VARYING AGE GROUPS

A remarkable, though rarely encountered type of condyloma acuminatum showing marked cell death was found among girls within the first decade of

Table 1 *Histological type and age distribution of condylomatous tumours of vulva, vagina, and penis seen in the biopsy service for all Uganda, 1964-75*

<i>Site/age group</i>	<i>Type of condyloma acuminatum</i>						
<i>(yr)</i>	<i>Common</i>	<i>Irregular</i>	<i>Flat</i>	<i>With cell death</i>	<i>With marked acanthosis</i>	<i>Dysplastic</i>	<i>Total</i>
Vulva and vagina							
0-9	3	2	—	11	—	—	16
10-19	14	19	1	1	12	—	37
20-29	8	4	2	—	3	1	18
30-39	2	—	—	—	1	2	5
40+	1	—	—	—	—	—	1
Total*	30	16	3	12	19	3	83
	<i>Common</i>	<i>Irregular</i>	<i>Flat</i>	<i>Proliferative (giant)</i>	<i>With marked acanthosis</i>	<i>Dysplastic</i>	<i>Total</i>
Penis							
0-9	7	1	—	—	—	—	8
10-19	27	5	—	—	9	—	41
20-29	36	6	1	—	10	1	54
30-39	4	2	—	1	—	—	7
40-49	3	1	1	3	—	2	10
50-59	3	1	—	4	—	5	13
60+	—	—	—	7	—	1	8
Total*	87	16	2	17	21	11	154

*Includes cases in which the age was not known or stated as 'adult' only.

Table 2 Histological type, frequency, mean and median age, and age range of condylomatous tumours of vulva, vagina, and penis compared to squamous cell carcinoma. All cases were collected through a biopsy service for all Uganda, 1964-75

Type of tumour	Vulva and vagina					Penis				
	No. of cases*	%	Age distribution (yr)			No. of cases*	%	Age distribution (yr)		
			Mean	Median	Range			Mean	Median	Range
Common CA	30	36.1	19.3	19	3-50	87	56.5	21.7	20	4-50
Flat CA	3	3.6	20.7	21	19-22	2	1.3	—	—	20, 30
Irregular CA	16	19.3	18.8	17	4-44	16	10.4	32.6	25	4-55
CA with cell death	12	14.5	5.7	5	2.5-10	—	—	—	—	—
CA with marked acanthosis	19	22.9	18.2	17	15-30	21	13.6	19.1	20	12-28
CA with dysplasia	3	3.6	28.3	30	20-35	11	7.2	47.1	46	22-62
Proliferative (giant) CA	—	—	—	—	—	17	11.0	55.4	55	31-80
Squamous cell carcinoma	185	—	45.6	45	7-78	1237	—	55.4	60	24-108

*Includes cases in which the age was unknown or stated as 'adult' only.
CA = condyloma acuminatum.

Fig. 1 Common condyloma acuminatum from a 5-year-old boy showing negligible vacuolation in other areas of tumour and little inflammatory stromal infiltration. Haematoxylin and eosin $\times 50$.

Fig. 2 Condyloma acuminatum of irregular outline occurring in a 27-year-old man. H and E $\times 12.5$.

life. Fibrovascular cores were seen superficially, but in deeper portions there was only a delicate stroma between the epithelial processes. Compared to the common condylomata acuminata the squamous cells were smaller and their nuclei more hyper-

chromatic. Acidophil bodies, usually termed dyskeratoses or cells undergoing monocellular keratinisation, were noted frequently in contrast to the remaining variants in which such changes were rarely seen. In one case, apparently due to shrinkage

Fig. 3 Flat condyloma acuminatum showing marked cytoplasmic vacuolation and moderate inflammatory infiltration in a 40-year-old man. *H and E* $\times$ 32.

and lysis of cells, large vacuoles and even vesicles filled with cellular debris had formed within the epithelial layer (Figs 4 and 5). This suggested that in these condylomata acuminata isolated cell necrosis is a prominent feature. Transitional epithelium was seen in eight of these cases in some areas of tumour, indicating the urethral orifice as the site of origin. The second most common variant, namely, condyloma acuminatum showing marked acanthosis, was observed in patients aged 12-30 years and displayed broad rete pegs with distinct cytoplasmic vacuolation in the upper epithelial strata.

In the following two groups of cases the risk of malignant degeneration is high. Invasive cancer, if present in other parts of the tumour, could have been overlooked, since biopsies only rarely show the entire lesion. Features used to describe one group of

Fig. 4 Isolated cell necroses and epithelial vacuoles seen in a condyloma acuminatum showing marked cell death in a 5-year-old girl. *H and E* $\times$ 210.

Fig. 5 Formation of vesicles filled with necrotic squamous cells. Same case as in Fig. 4. *H and E* $\times$ 76.

cases were often found to occur together. Proliferative changes were frequently in addition dysplastic, and irregular rete ridges were seen in cases of

dysplastic and proliferative condylomata acuminata.

Condylomata acuminata showing dysplastic changes were rarely found but were more frequently on the penis than on the vulva and vagina and occurred only in the higher age groups. Features of dysplasia were seen combined with a loss of, or an increase in, differentiation of the squamous epithelium. One case included in this group was from a 56-year-old man and showed bowenoid changes resembling a carcinoma *in situ*.

Another rare tumour was proliferative (giant) condyloma acuminatum. These cases occurred only on the penis and showed the highest age range of all condylomatous tumours. The patients were between 40 and 70 years old except for two aged 31 and 80 years. These lesions scarcely precede the cases of penile cancer in age distribution. A difference is noted only when the median age is compared (Table 2).

The term proliferative was preferred since the size of the tumour cannot be known from specimens received in small bottles from up-country hospitals. According to the enclosed clinical description, five of the 17 cases were sores or swellings, three were papillary tumours, and in six the characteristic appearance of giant condyloma was noted, namely, a large, fungating growth destroying the organ; in two cases no details had been given. One case, seen in its dimensions on the histological section, showed clearly that there are also small tumours displaying features typical of giant condyloma.⁷⁻⁹ Well-circumscribed downgrowth of the rete ridges could be seen, but no true invasion. In the example shown in Fig. 6 there was a transition from a vacuolated condyloma acuminatum to a lesion resembling a verrucous carcinoma, except that the large islands of tumour were still connected with each other through epithelial bridges.

Fig. 6 Proliferative (giant) condyloma acuminatum from a 67-year-old man showing transition to verrucous carcinoma in an area of large epithelial islands still connected with each other through epithelial bridges. H and E $\times 12.5$.

VACUOLATION AND INFLAMMATION

To delineate further the variants of condyloma acuminatum these features proved to be useful. No differences were found between males and females, and the results were therefore combined for both sexes (Table 3). It is noteworthy that in the common type, and in lesions showing marked cell death, cases with negligible vacuolation were often encountered. Cytoplasmic vacuolation was most marked in condylomata acuminata showing marked acanthosis, whereas irregular, dysplastic, and proliferative lesions showed the least degree of such a change. The number of observations is small in the older age groups (Table 1), but marked differences in the age-specific proportions of vacuolated cases were not noted in the groups of common and irregular condylomata acuminata.

MALIGNANT DEGENERATION

Seven cases of penile cancer were found in the files with a previous biopsy report of condyloma acuminatum.¹² On re-examination all cases were condylomata acuminata, one showing slight vacuolation, five dysplastic and two additional proliferative changes; six were in the older age groups and, in subsequent biopsies taken within a mean time interval of six months, showed progression towards cancer, ranging from severe dysplasia to invasive carcinoma. In the seventh case, a 26-year-old patient showing moderately vacuolated condyloma acuminatum, a carcinoma had developed after a period of eight years; however, it remained uncertain whether the biopsies came from the same patient.

Discussion

Comparisons of age distribution, a commonly used tool to confirm the precancerous nature of any lesion, have rarely been recorded for cases of condyloma acuminatum. Apart from the terminology, this survey is in agreement with a small series of cases of squamous papillary tumours from

the uterine cervix. Fifteen cases of condyloma acuminatum showing cytoplasmic vacuolation were from patients between 15 and 29 years of age except for one 50-year-old patient, whereas four cases of squamous papilloma with coexisting dysplasia or carcinoma-in-situ were from the 28-49 years age group and showed negligible vacuolation only.⁴

Another report, comparing cases of giant condylomata acuminata, noted a progression in age towards lesions called malignant condyloma and solid papillary epithelioma; the mean ages were 63, 64, and 66 years, respectively. However, the mean age of cases of overt squamous cell carcinoma was only 60 years.¹⁴ Moreover, in a previous series of cases from Uganda, the mean age of four patients with giant condylomata acuminata and 32 with squamous cell carcinomas was 53.7 and 56.6 years, respectively,⁹ a result not unlike that from our series of cases. Thus, the similarity in age distribution (Table 2) does not argue against the view that proliferative condylomata acuminata precede cases of verrucous carcinoma. There may be certain types of squamous cell carcinoma which occur in younger age groups than these papillary tumours.

Only three dysplastic and no proliferative variants of condyloma of the vulva and vagina were found in this biopsy survey, but there were 28 such cases of the penis. This is not surprising, since in Uganda patients tend to come to hospital at a late stage of the disease when the cancer may have overgrown the condylomatous lesion, and on the vulva and vagina the incidence of cancer is much lower than on the penis. No adequate explanation was found why condylomata acuminata showing marked cell death occurred solely among girls and in the majority of cases near to or on the opening of the urethra.

The two groups of cases in the age distribution already noted in previous investigations show different frequencies of the variants of condylomatous tumours (Tables 1 and 2).¹² One of the tentative conclusions reached, namely, that condylomata acuminata occurring in the age group 40 years and

Table 3 *Cytoplasmic vacuolation and density of stromal inflammatory infiltration of condylomatous tumours of vulva, vagina, and penis recorded in the biopsy service for all Uganda, 1964-75*

Type of tumour	No. of cases	Vacuolation* (%)			Inflammation* (%)		
		I	II	III	I	II	III
Common CA§	117	25	55	20	35	48	17
Irregular CA†	32	58	42	—	19	45	36
CA with marked cell death‡	12	22	39	39	17	83	—
CA with marked acanthosis‡	40	3	47	50	5	50	45
CA with dysplasia	14	69	23	8	15	23	62
Proliferative (giant) CA	17	79	21	—	—	13	87

*Degree of vacuolation and inflammation: I negligible, II moderate, III marked.

† I, ‡ 2, § 7 cases in which the degree of inflammation could not be measured because little stroma was seen at the base of the tumour. The few cases of flat condyloma acuminatum are not listed.

over show a high risk of subsequent carcinoma, can be confirmed. In the majority of cases proliferative changes were found characterised by a destructive downgrowth and a marked decrease in the stromal component between the rete ridges at the base of the tumour and/or dysplastic changes. Furthermore, two other features were observed more frequently in variants occurring in the older age group: these were a decrease in cytoplasmic vacuolation and an increase in the density of the inflammatory stromal infiltrate. It could be, therefore, that these changes are signs of an increase in tumorous proliferation and indicate an increased risk of malignancy (Table 3).

This transition in histological appearance with increasing age is a reason for discontinuing the distinction of separate and unrelated entities of squamous papillary tumours differing in risk of progressing to subsequent cancer. Cytoplasmic vacuolation, often taken as a sign of viral infection and therefore believed to be characteristic only of condyloma acuminatum and not of squamous cell papilloma, was seen occasionally in dysplastic and proliferative tumours (Table 3). In addition to the case of malignant degeneration and the example illustrated in Fig. 6, there are a number of reports of vacuolated condylomata acuminata with simultaneous or subsequent dysplastic, proliferative, and cancerous change.¹⁵⁻²⁰ All these observations are compatible with the view that dysplastic and proliferative condylomata acuminata may arise from the types of tumour seen in young patients. However, such a coincidence and transition have been noted only rarely, and some condylomata acuminata occurring in young people showed only negligible and thus perhaps non-specific vacuolation (Table 3). It cannot be ruled out, therefore, that there are papillary squamous tumours that show no abnormal cytoplasmic vacuolation throughout their development towards cancer.

Recently, traces of a human papillomavirus type 2 were found in two patients with verrucous carcinoma including, in one instance, a condylomatous area of tumour.²¹ Apart from this as yet unconfirmed report, there is an epidemiological observation which favours the view that the conditions are related.¹² In Uganda, a geographical correlation of condylomata acuminata with cancer was found in the 18 districts of the country for both age groups. Furthermore, experiments show that the SV 40 virus, which is from the same group of papova-viruses as the agent found in condyloma acuminatum,²² can infect and kill the cell or leave it viable and transform it.²³ It is tempting to assume, therefore, that cyto-cidal and vacuolating viral infections occurred predominantly in young people, particularly in the group of condylomata acuminata showing marked

cell death, whereas with increasing age, when cytoplasmic vacuolation becomes less marked, the other type of infection prevailed.

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