Cervical Lesions in Patients with Malignant Melanoma

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Koilocytes were found in the cervical epithelium in association with cervical intra-epithelial neoplasia in 8 out of 9 cases of malignant melanoma. This suggests that the cervical lesion in them was of viral origin. In 62 women with malignant melanoma but without cervical atypia there was also an excess of koilocytosis compared with controls with neither lesion. These findings point to the possibility that human papilloma virus infection may also be involved in the development of malignant melanoma, as it has been shown to be in cervical intra-epithelial neoplasia. (Received August 6, 1988.)

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In a study of 805 women with cervical dysplasia we recently found 3 patients with malignant melanoma (1). This is a 6-fold over-representation compared with the incidence in all women in this district. Conversely in 71 women with malignant melanoma from whom gynaecological cytology was available, the incidence of cervical intra-epithelial neoplasia (CIN) was 8 times that expected on the basis of case-matched controls (2).

This association had not been reported previously. It suggests a possible aetiological link between the two conditions. The nature of such a link is unknown although a viral aetiology was postulated. In a search for further data we have studied the cytological and histological findings in the cervical lesions from these 9 cases with both malignant melanoma and CIN, and compared them with those in a series of controls.

MATERIAL AND METHODS

Cytology

Smears from the cervix/fornix (fixed with an aerosol fixative and stained with Papanicolaou's stain) were screened for the presence/absence of koilocytes (3) (see Fig. 1*a*).

The smears were from (i) the 9 patients with malignant melanoma and CIN, and (ii) the 62 patients with malignant melanoma but without CIN, that have been reported previously (2). The latter had been selected, on the basis of the availability of gynaecological cytology, from a total of 213 women with malignant melanoma diagnosed at this Institute in 1981–84 inclusive.

In addition a prospective study was set up (over 2 1/2 months from mid-October to the end of December 1986) in which incoming gynaecological cytological specimens were routinely screened for koilocytes.

Histology

Routine slides (formalin-fixed, paraffin-embedded material, stained with haematoxylin, eosin and saffran) were available from the uterine cervix in 7 of the 9 cases of malignant melanoma with cytological CIN. These were reviewed for the presence/absence of koilocytes (4) (see Fig. 1*b*). Histological material was also available from all 9 malignant melanomas from patients with CIN and was reviewed.

RESULTS

The cervical findings, both cytological and histological, in the 9 cases of malignant melanoma and CIN are related to the year of diagnosis of malignant melanoma in Fig. 2.

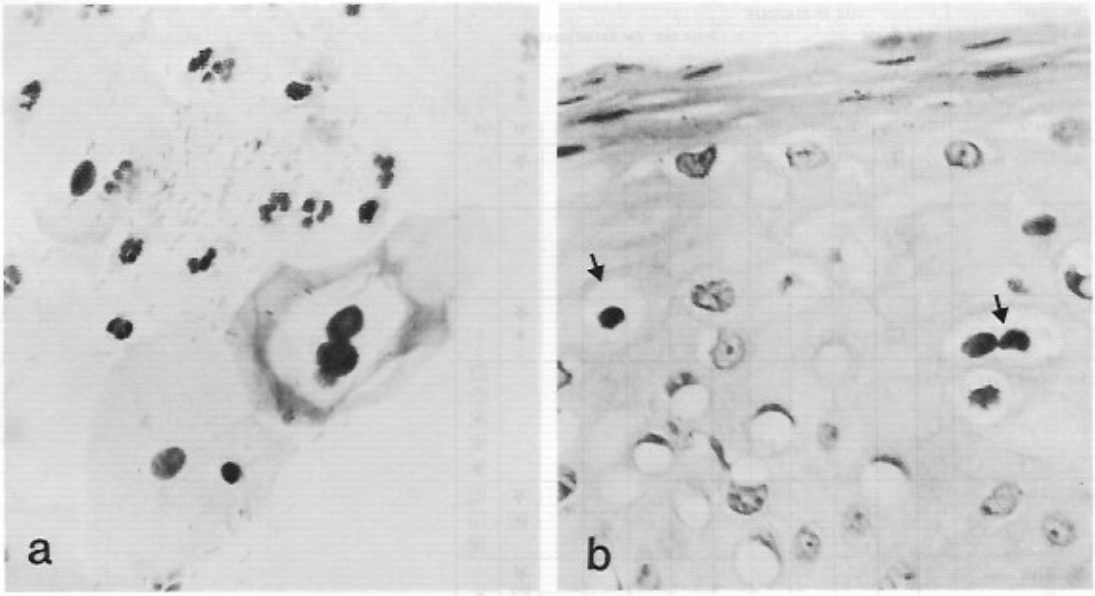

Fig. 1. (*a*) Cervical smear showing koilocytosis. Note: Perinuclear clearing and peripheral condensation of the cytoplasm of the binucleate squamous epithelial cell. Papanicolaou, ×325. (*b*) Cervical biopsy showing koilocytosis. Note: A binucleate cell (*arrowed*). as in (*a*), and other squamous cells showing perinuclear clearing. HES, ×325.

In 8 of the 9 cases, koilocytes were recorded in at least one smear. In 4 cases the smear showing koilocytes also showed CIN. There was considerable scatter, however, the longest interval being 9 years. The mean interval between the two events was 1.7±3.1 years. There was a similar scatter in the interval between the recording of koilocytosis and the diagnosis of malignant melanoma. In 2 cases these events occurred simultaneously and again the longest interval was 9 years. The mean was 2.1±2.9 years.

In the 124 cytological specimens from the 62 women with malignant melanoma but no smear showing atypia, koilocytes were found in a total of 6 specimens from 4 women (4.8%). In contrast, 12 of the 44 smears from the 9 women with malignant melanoma and CIN showed koilocytosis. In 4, CIN and koilocytosis occurred in the same smear. Although the number of cases is low in the test group, and the number of smears/patient differs in the two groups, the difference in the number of slides with/without koilocytosis is statistically significant (χ^2 with Yates' correction = 14.8, $p<0.0005$).

Cervical histology was available in 7 of the 9 cases (see Fig. 2). In 5 cases, 1 or 2 biopsies showed both CIN and koilocytosis in the same slide, one showed koilocytosis without CIN. Case 1 showed neither koilocytosis nor CIN.

When these histological findings as well as the cytological ones are taken into consideration, koilocytosis was recorded in the same year as CIN in 7 cases, the interval being 9 years in the 8th case. Koilocytosis was recorded in the year the melanoma was diagnosed in 4 cases, the mean interval being 1.9±3.1 years.

In case 9 the cervical dysplasia recorded in one smear from 1985 was slight. There was no histology in this case. Thus it may or may not be relevant to the present study.

The prospective study showed that in the absence of CIN, 89 of 9306 smears showed koilocytes, i.e. under 1%, while 86 of 268 slides with CIN (32%) showed such changes.

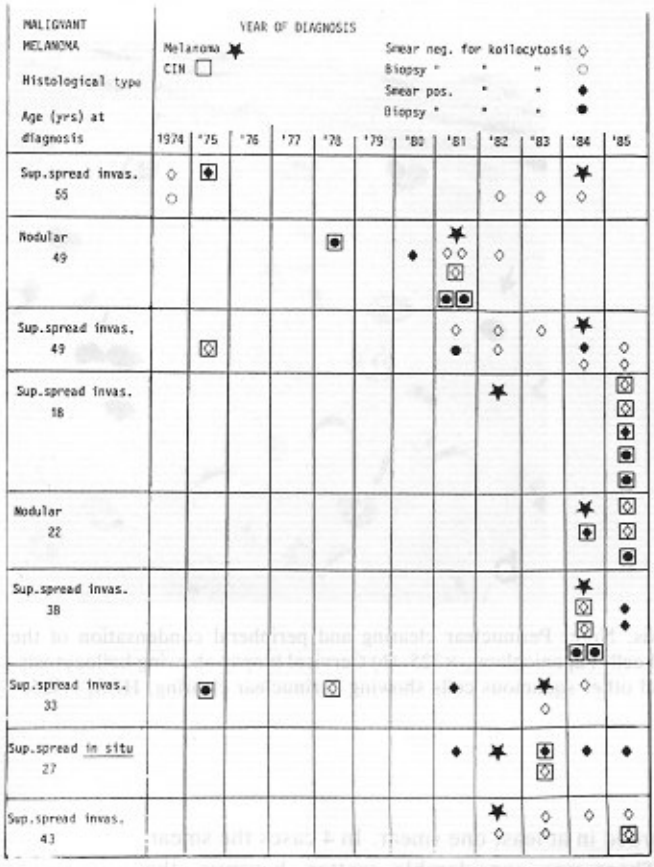

Fig. 2. The cytological and histological findings in the uterine cervix of 9 women with malignant melanoma, related to the year of diagnosis.

DISCUSSION

Koilocytes are the trademark of human papilloma virus in the cervical epithelium (5). The condition was first described in 1956 (6), but its significance was not recognized for many years (7). The association of koilocytosis (and hence virus infection) with CIN is now well established (8). The 32% incidence of koilocytosis in patients with CIN but without melanoma is lower than in other reports (3, 5), as is the 1% found in otherwise normal cervical smears in our material. Against this background the finding of koilocytic lesions in 8 of 9 patients with CIN and malignant melanoma is striking.

The 'empty' perinuclear areas seen in the koilocytes, that give the cells their name, have contained the virus (4). It may however be present in a different form in cells that do not show such changes (8, 9). It has also been demonstrated at a distance (cm) from such cervical lesions in presumably normal tissue (10). On this basis it is not surprising that the koilocytic lesions reported here did not occur consistently in a given case, but were found with or without atypia at various time in the different cases. It may also be pertinent here that virus-induced laryngeal papillomatosis has been reported in the children of mothers with genital warts at delivery (11). Thus infection may be spread from one tissue to another, and a latent interval may be involved. In the present cases the mean interval was about 2 years, for both melanoma and CIN.

It is also of note that the increased incidence of koilocytes in the cervical smears without atypia from patients with melanoma, compared with the controls without atypia or

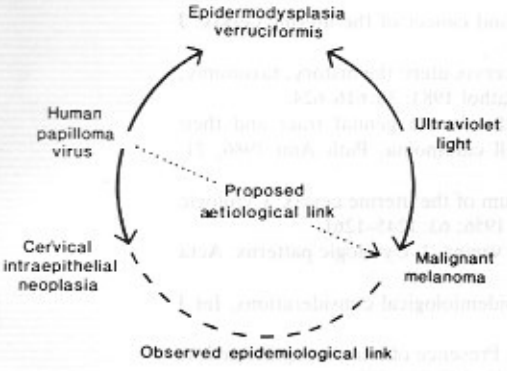

Fig. 3. Established connections between human papilloma virus infection and ultraviolet light in the aetiology of cervical intra-epithelial neoplasia, epidermodysplasia verruciformis, and malignant melanoma (——), related to the observed (– – –) and proposed links (. . . . .) described in this paper; see text.

melanoma, is in keeping with the excess of CIN in patients with melanoma as a whole, as we have reported previously (2). There are no other reports on the incidence of koilocytosis in patients with malignant melanoma.

Some years ago an increase in the incidence of malignant melanoma was reported in oral contraceptive users compared with non-users (12). This could not be explained at the time, but hormonal factors could be involved. So too could exposure to human papilloma virus infection. It has also been reported that human papilloma virus infection may occur more readily in patients with immunodeficiency (5, 13) and that this may be relevant to the development of CIN. However, the immune status of patients with malignant melanoma is said to be intact with early lesions, although it may be impaired in those with metastases (14).

The part played by ultraviolet light in the development of malignant melanoma is well established (15), but it is not necessarily the whole story. Our findings suggest that yet another factor may be involved: human papilloma virus infection. This does not exclude the action of ultraviolet light, but may indeed be dependent on it. In the rare condition epidermodysplasia verruciformis, in which human papilloma virus is involved, skin malignancy does not develop in the absence of ultraviolet light (16). There may be a parallel here. Both papilloma virus and ultraviolet light, acting in synergism, may be prerequisites for the development of malignant melanoma (see Fig. 3). This too would be in keeping with the theory that human papilloma virus alone is not capable of giving rise to neoplasia, but that other initiating factors may be required (17).

The increase in the incidence of malignant melanoma in recent years may thus not be due entirely to changes in habits related to exposure to ultraviolet light. Exposure to the human papilloma virus may be as important.

ACKNOWLEDGEMENT

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