Cellular Changes in Severe Dysplasia of the Uterine Cervix Progressing to Malignancy

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Yajima, A., Higashiiwai, H., Sato, A., Watanabe, M., Mori, T., Yonemoto, Y. and Hosshi, K. Cellular Changes in Severe Dysplasia of the Uterine Cervix Progressing to Malignancy. Tohoku J. Exp. Med., 1979, 129 (1), 75-81 — Of a total of 1321 cases of severe dysplasia of the uterine cervix, 237 lesions (18%) were found by punch biopsy and cytological examination to have progressed to carcinoma in situ or microinvasive carcinoma later in the course of follow-up. The changes in exfoliated cells during the progression to malignancy were examined in 95 of the 237 cases. Results obtained were as follows: (1) The ratio of parabasal (immature) cells to the whole dysplastic cells gradually increased in each specimen. (2) Immature dysplastic cells showing increased nuclear membrane tension and irregular staining of the nuclear membrane gradually increased. (3) The number of immature dysplastic cells with finely or coarsely granular chromatin patterns gradually increased.

MATERIALS AND METHODS

Among 1321 patients with severe dysplasia, 95 cases which have progressed to malignancy and 55 regressed cases were available for examination. The investigation was made in terms of the following three categories: (1) the discovery rate of immature dysplastic cells in each specimen, (2) findings on the nuclear membrane of immature dysplastic cells, and (3) the chromatin pattern of immature dysplastic cells.

Cellular sampling was done in all cases by the scraping of the portio vaginalis and cervical canal with an Ayre-type wooden spatula. Staining was performed using Papanicolaou's method.

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RESULTS

The number of women examined by mass survey for cervical cancer in Miyagi Prefecture from 1961 until 1975 and the number of discovered lesions are shown in Table 1. The discovery rates of carcinoma in situ, microinvasive carcinoma and severe dysplasia were 0.13%, 0.13% and 0.41%, respectively.

Of the 2264 cases in which severe dysplasia was discovered, 1321 were followed up by the Bureau of Cancer Control. Among these 1321 women, the lesions of 237 (18%) were found to have progressed to carcinoma in situ or microinvasive carcinoma within four years from the discovery of the dysplasia, and the lesions of 521 (39%) regressed, that is, both cytological examination and punch biopsy had turned negative for dysplasia (Table 2).

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<th>Table 1. Number of cases and detection rates of invasive carcinoma, carcinoma in situ and severe dysplasia of the uterine cervix (1961–1975)</th>
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<td>Invasive carcinoma</td>
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<td>Number of cases</td>
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<td>Detection rates</td>
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<th>Table 2. Follow-up of 1321 cases of severe dysplasia (1961–1975)</th>
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<td>Progression</td>
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The ratios of immature dysplastic cells to the whole dysplastic cells in the courses of follow-up are expressed diagrammatically in Fig. 1 for 95 cases which had progressed to carcinoma in situ or microinvasive carcinoma and 55 cases which had regressed. Through the retrospective examination, it was found that in the progressed cases the ratio began to increase 14 months before the final diagnosis. In the regressed cases, the ratio decreased gradually.

The changes in chromatin pattern during the malignant development of immature dysplastic cells are expressed in Fig. 2. The majority of immature dysplastic cells at the time of discovery of the dysplasia had finely reticular chromatin in 19 cases, coarsely reticular chromatin in 38 cases and finely granular chromatin in 38 cases. No cases showed coarsely granular chromatin. In contrast, in the cases in which carcinoma in situ or microinvasive carcinoma was discovered, the chromatin pattern was finely reticular in no cases, coarsely reticular in 28 cases, finely granular in 62 cases and coarsely granular in 5 cases.

In the cases showing regression of the dysplasia, the chromatin pattern at the time of discovery of the severe dysplasia were finely granular in 17 cases, finely reticular in 9 cases and coarsely reticular in 29 cases. At the time of the
Fig. 1. Ratio of parabasal to whole dysplastic cells accompanied with progression or regression of dysplasia. A-B, indefinite; B-C, 14 months on average; B-D, 18 months on average.

![Graph showing ratio of parabasal to whole dysplastic cells over time.]

Fig. 2. Changes in chromatin patterns of parabasal dysplastic cells in cases which progressed from dysplasia to malignancy.

![Bar graph showing changes in chromatin patterns over time.]

disappearance of dysplasia, there were 0, 17 and 38 cases, respectively (Fig. 3).

The changes in the nuclear membrane in the progressed cases are shown in Fig. 4. The nuclear membrane at the time of discovery of the severe dysplasia was flaccid and evenly stained in 54 cases, stretched tight and spherical in 17 cases, stretched tight and unevenly stained in 19 cases and unevenly stained in 5 cases. In contrast, at the time of discovery of carcinoma in situ, there were 5, 23, 50 and 17
Fig. 3. Changes in chromatin patterns of parabasal dysplastic cells in regressed cases.

Fig. 4. Changes in configurations of nuclear membrane of parabasal dysplastic cells in cases which progressed from dysplasia to malignancy.
Fig. 5. Changes in configurations of nuclear membrane of parabasal dysplastic cells in regressed cases.

On the other hand, among the cases showing regression, there were 5 cases showing unevenly stained nuclear membranes, 19 stretched tight cases, and 31 flaccid and evenly stained cases, whereas at the time of disappearance of the dysplasia, there were respectively 0, 2, and 53 such cases (Fig. 5).

The above-discussed findings are expressed schematically in Fig. 6.
DISCUSSION

It is clinically extremely convenient to classify dysplasia of the uterine cervix into low degree (mild) and high degree (severe) dysplasia (Wied 1962), since it is known that only 0.3% of cases of mild dysplasia progress to malignant lesions (Noda 1975), whereas roughly 20% of cases of severe dysplasia do so. Consequently, it would be wise to call only severe dysplasia a precancerous lesion of cervical cancer. When it is impossible to follow-up cases of severe dysplasia, it is generally accepted that therapeutic conization should be performed immediately. If, on the other hand, some consensus can be reached between the doctor and patient, it is better to follow-up the subsequent courses. It is found by the careful follow-up study that approximately 40% of such lesions have regressed and only roughly 20% demand treatment.

Previously, several studies (Okagaki et al. 1962; Kehar and Wahi 1967; Komori et al. 1973) have reported that the number of immature dysplastic cells appearing in cytological samples gradually increases with the progression of dysplasia to malignancy. According to the results of the present study, the number of immature dysplastic cells continues to increase over a roughly 15 month period and, in cases in which the number of immature dysplastic cells reaches 80% of the total number of dysplastic cells, carcinoma in situ is detected histologically without exception.

There are also many reports (Takeda and Kaida 1968; Shibata and Ichihara 1971; Shimotomai and Nishiya 1971) suggesting that thick staining of the nuclear membrane of dysplastic cells occurs together with the progression of dysplasia to malignancy. Such thick staining is fundamentally the same phenomenon as the change from reticular to granular chromatin and likely reflects an increase in chromatin. Furthermore, the irregular distribution of chromatin found at an early stage can also be interpreted as irregular staining of the nuclear membrane (Timonen and Kauraniemi 1967; Kehar and Wahi 1967; Wahi et al. 1969; Tenjin 1972). Consequently, it would be extremely useful to construct a chart for the continued observation of the number of immature dysplastic cells, chromatin pattern and condition of the nuclear membrane of immature dysplastic cells in order to facilitate the follow-up of dysplasia. By undertaking the follow-up of such cases in this way, it should be possible to check whether or not the dysplasia has developed to an irreversible state before it has actually progressed to carcinoma in situ or microinvasive carcinoma.

References


