E-cadherin expression during progression of squamous intraepithelial lesions in the uterine cervix

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Summary

Alterations of E-cadherin expression in cervical intraepithelial neoplasias and invasive carcinomas of the uterine cervix have been described by some authors but their clinical significance has not yet been clarified.

Archival specimens of 27 normal cervical epithelia, 15 atypical cells of undetermined origin (ASCUS), 53 low-grade squamous intraepithelial lesions (LSIL), 19 high-grade squamous intraepithelial lesions (HSIL) and six invasive squamous carcinomas were evaluated for E-cadherin expression. The cytological material was processed using liquid based cytology (ThinPrep technique) and immunostained for E-cadherin. All HPV infections (koilocytes) showed strong cell membranous E-cadherin expression. In HSIL a strong decrease in E-cadherin expression and heterogeneous distribution was noticed. In the relatively small number of squamous cell carcinomas of the cervix studied, a significant decrease or loss in E-cadherin expression, predominantly cytoplasmic, was noted. We concluded that decreased E-cadherin expression appears to be a useful parameter of malignant potential of cervical lesions. E-cadherin immunoexpression could provide an additional criterion in correlation with cyto- and histomorphology and colposcopy to define high grade CIN lesions.

Key words: Immunocytochemistry; E-cadherin; Intraepithelial lesion.

Introduction

Cadherins are a family of transmembrane glycoproteins involved in homotypic calcium dependent intercellular adhesions and have a critical role in cell sorting and tissue formation during organogenesis. Cell-cell adhesion mediated by E-cadherin is often lost or disturbed in human carcinomas. Moreover, it has been postulated that E-cadherin loss may be important in tumor spread.

E-cadherin, a representative member of this subfamily, is responsible for cell-cell interactions of epithelial cells and plays an essential role in the generation and maintenance of epithelial cell polarity.

Alterations of E-cadherin expression in cervical intraepithelial neoplasias and invasive carcinomas of the uterine cervix have been described by some authors [2, 3, 5] but their clinical significance has not been clarified up to now.

The purpose of this paper was to investigate E-cadherin expression in correlation with cytomorphology in intraepithelial and invasive lesions of the uterine cervix.

Materials and Methods

Archival specimens of 27 normal cervical epithelia, 15 atypical cells of undetermined origin (ASCUS), 53 low-grade squamous intraepithelial lesions (LSIL), 19 high-grade squamous intraepithelial lesions (HSIL) and six invasive squamous carcinomas were evaluated. The cytological material was processed using liquid based cytology (ThinPrep technique) and immunostained using monoclonal antibody for specific E-cadherin (clone 36B5 Novocastra Newcastle upon Tyne U.K).

The Thin prep involves a new technique for the collection and the preparation of cervical cytology specimens. Immunocytochemistry was performed on smears and tissue sections using the Ventana Nex Es Automated slide stainer and related Ventana reagents.

E-cadherin immunoexpression was correlated with the corresponding cytologic and histologic diagnoses when available (in all of HSIL and in one/third of LSIL). The pattern of distibution and the intensity of E-cadherin immunostaining were assessed by two independent observer cytopathologists. All HPV infections (koilocytes) showed strong cell membranous E-cadherin expression except for one case. In HSIL a strong decrease in E-cadherin expression and heterogeneous distribution was noticed. In some cases an almost complete loss of E-cadherin expression was found in the basal and parabasal cells with expression being partly restored in the suprabasal layer cells.

Results

Our results are analyzed in Tables 1, 2 and 3. Membranous as well as cytoplasmic staining of E-cadherin expression was evaluated and the findings were similar in both cytologic and histologic specimens. According to the E-cadherin immunoreactivity the lesions were classified as follows: negative, weak and strongly positive.

All samples of normal cervix epithelium were positive for E-cadherin membranous expression of the basal and parabasal cells. Only in a few basal cells was a weak homogenous cytoplasmic staining observed.

The presence and localization of E-cadherin expression was closely correlated with the grade of the CIN lesions.

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g. 1

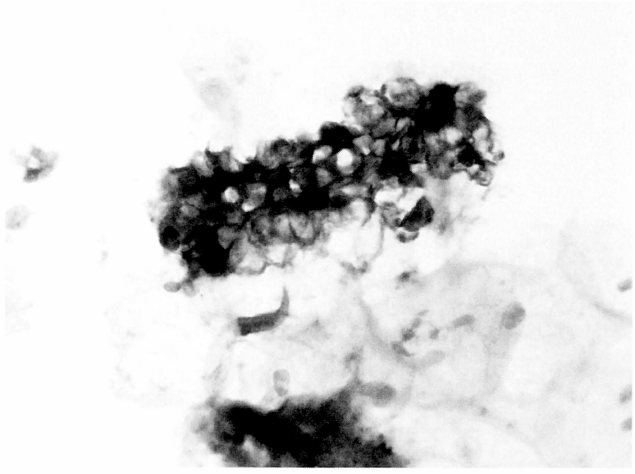

Fig. 2

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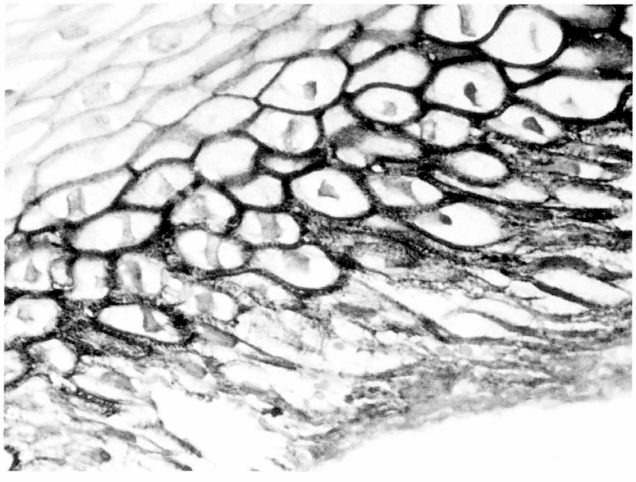

Figure 1. — ThinPrep technique. Positive membranous expression of E-cadherin in LSIL (x 400).

Figure 2. — ThinPrep technique. Positive membranous and cytoplasmic expression of E-cadherin in HSIL (x 400).

Figure 3. — Tissue section. Positive membranous expression of E-cadherin (x 250).

Table 1.

No. of cases	Cytologic Diagnosis
27	Negative
15	ASCUS
53	LSIL
19	HSIL
7	Invasive
Total: 121	

Table 2.

	E-Cadherin immunoexpression	
Type of lesion	Weak	Strong
Negative	9	18
ASCUS	7	8
LGSIL	21	32
HGSIL	15	4
Invasive	5	2

Weak E-Cadherin expression included ± (< 10%), 1+ (< 30%) of cells; Strong E-Cadherin exression included 2+ (30-60%), 3+ (> 70%) of cells

Table 3.

	E-Cadherin Reactivity Pattern	
Type of lesion	Membranous	Cytoplasmic
Negative	+	–
ASCUS	+	–
LSIL	+	–
HSIL	–	+
Invasive	–	+

No substantial decrease in E-cadherin expression was noted in LSIL. However, a relatively increased intracellular staining was noticeable in the proliferating layers of cells in the lesions.

In the tissue sections of low-grade lesions the specific E-cadherin immunostaining was consistently localized within two-three cell layers from the basement membrane but it was not always homogeneously distributed.

Actively proliferating cells of immature squamous metaplasia were marked by an increase in intracellular staining for E-cadherin, although the presence of a large amount of E-cadherin at cell-cell boundaries was still clearly evident. Areas of squamous metaplasia showed a heterogeneous expression of E-cadherin and the immunostaining appeared to be less intense in more immature squamous epithelium. E-cadherin expression in reserve cells was noted in relation to the development of a reserve cell metaplasia.

All HPV infections (koilocytes) showed strong cell membranous E-cadherin expression except for one case. In HSIL a strong decrease in E-cadherin expression and heterogeneous distribution was noticed. In some cases an almost complete loss of E-cadherin expression was found in the basal and parabasal cells with expression being partly restored in the suprabasal layers cells. This event

was more evident in tissue sections. In the relatively small number of squamous cell carcinomas of the cervix studied, a significant decrease or loss in E-cadherin expression, predominantly cytoplasmic, was noted.

Discussion

Squamous epithelial cells of the ectocervix are tightly bound to each other and to the basement membrane through desmosomes and tight junctions owning to a number of adhesion molecules. E-cadherin is one of the major cell adhesion molecules defining the architecture and differentiation of keratinocytes.

It is known that in CIN there is a change in cell adhesion molecule expression from the exclusively basilar distribution seen in normal squamous epithelium to an aberrant distribution that encompasses the entire epithelial layer, including the surface. This suggests that decrease or eventual loss of E-cadherin expression in cervical neoplasia may correlate with aggressive behavior and progression.

However, it should be taken into account that squamous intraepithelial lesions even with a high degree of atypia, may regress in a large percentage of cases. The different patterns of E-cadherin expression are clearly correlated with different cyto- and histological features of each separate type of lesion. Our findings are in agreement with observations reported in previous studies. Vessey *et al.* found an increasing tendency for E-cadherin to be expressed in the cytoplasm as the grade of squamous intraepithelial lesion increased mainly in invasive squamous carcinomas. The cytoplasmic and partly membranous E-cadherin expression in HSIL and invasive carcinomas could be explained from the effect that even in metastatic tumor cells there is some evidence of persistent cell-cell adhesion [2]. Hypermethylation has been proposed as an explanation for the decreased protein expression [1].

In conclusion:

1) Decreased E-cadherin expression appears to be a useful parameter of the malignant potential of cervical lesions.

2) E-cadherin immunoexpression could provide an additional criterion in correlation with cyto- and histomorphology and colposcopy to define high-grade CIN lesions.

3) Especially membranous or cytoplasmic E-cadherin expression would be of diagnostic and prognostic value in precancerous and cancerous lesions of the uterine cervix.

4) The ThinPrep method is more effective than conventional techniques and is considered to be a superior screening test in the detection of precancerous changes of the cervix. Consequently, it gives the possibility of using easier immunocytochemistry [4].

5) Hopefully, further studies of cadherins will continue to provide useful information for diagnosis, and possibly unravel targets for future therapeutic strategies of squamous intraepithelial lesions.

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