The expression of epithelial specific antigen in cervical intraepithelial neoplasia and adenocarcinoma

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Summary

There is a spectrum of changes described as cervical glandular intraepithelial neoplasia (CGIN) with adenocarcinoma in situ (AIS) considered to represent the most severe lesion in that spectrum. Although there is evidence to suggest a progression of CGIN to AIS and to invasive adenocarcinoma, the natural history of these potential precursor lesions has not been fully elucidated. The aim of this project was to establish the relationship of endocervical glandular intraepithelial neoplasias to uterine endocervical adenocarcinoma.

Our study included 40 cases of glandular lesions of the cervix (15 cases of endocervical glandular intraepithelial neoplasia, eight of adenocarcinoma in situ and 17 cases of invasive adenocarcinoma). An attempt was made to examine the immunohistochemical localization of epithelial specific antigen (ESA) in those lesions and compare the results with ten cases of normal endocervical epithelium.

ESA showed positive staining of the basolateral membrane of endocervical cells in the normal endocervix. The expression of ESA was found to increase from the basolateral to the diffuse cytoplasmic membrane in 12 out of 15 cases of CGIN (80%), in seven out of eight cases of AIS (84%) and in all of the 17 invasive adenocarcinomas (100%). This finding indicates that ESA is a useful marker in the diagnosis of glandular intraepithelial neoplasia and suggests that CGIN and AIS may be precursor lesions of cervical adenocarcinoma.

Key words: Cervical glandular intraepithelial neoplasia; Epithelial specific antigen; Adenocarcinoma.

Introduction

There have been both relative and proposed absolute increases in the incidence of "adenocarcinoma of cervical origin" among women under 35 years of age [1], currently estimated to be 10-20% of all invasive cervical cancers. It is difficult for the pathologist to diagnose cervical adenocarcinoma based on PAP smears, because the cytologic features of early lesions are found to be located higher in the endocervical canal [2].

Although there is evidence that CGIN progresses to AIS and to invasive cancer, it is still questionable whether the glandular dysplasia is a precursor lesion of the malignant component [3, 4]. Many cases with frank AIS will also exhibit changes of CGIN in other areas. Cases with only CGIN are much less common, suggesting that the time of progression from CGIN to AIS may be short. In contrast, progression from AIS to frankly invasive adenocarcinoma may be quite long. (Some authors believe that this may occur eight to 14 years following diagnosis of AIS) [5].

CEA positivity is a helpful marker in distinguishing adenocarcinoma of the cervix from benign lesions. CEA is negative in normal endocervical mucosa and in most benign lesions of the cervix but no reactivity of CEA is mentioned in endocervical glandular dysplasia [3, 4]. In order to prove the relationship between CGIN and adenocarcinomas and to evaluate whether CGIN could represent a precursor lesion of adenocarcinomas we used another marker, the epithelial specific antigen (ESA) which has been reported in tumors of skin appendages [6, 7].

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Material and Methods

We examined tissue blocks from 40 cases of cervical glandular lesions. Our material consisted of 17 specimens of invasive adenocarcinoma, eight specimens of adenocarcinoma in situ and 15 specimens of endocervical glandular intraepithelial neoplasia. The results were correlated with ten specimens from normal endocervix. All tissue blocks were fixed in 10% formalin and embedded in paraffin.

Immunohistochemical procedures

We used the streptavidin-biotin complex method. A minus (–) to plus (+) grading system was used to quantify immunostaining (– negative, + positive).

Results

The epithelial specific antigen was positive in the lateral basement membrane of the endocervical cells in all ten cases of normal endocervical tissue. The ESA staining was found to increase from the basolateral membrane to the diffuse cytoplasmic membrane in most endocervical intraepithelial neoplasias.

Thus, ESA was positive in 12 out of 15 cases of CGIN, seven out of eight cases of AIS, while all 17 cases of invasive adenocarcinoma of the cervix strongly expressed ESA on both lateral and cytoplasmic membranes.

The staining intensity and distribution of ESA are summarized in Table 1 (normal endocervix), Table 2 (CIN), Table 3 (in situ adenocarcinoma) and Table 4 (invasive adenocarcinoma).

Table 1. — *Expression of ESA immunoreactivity in normal endocervices.*

Case	Age (years)	ESA	
		Baso	Cyto
1	54	+	–
2	35	+	–
3	45	+	–
4	42	+	–
5	37	+	–
6	50	+	–
7	46	+	–
8	33	+	–
9	48	+	–
10	44	+	–

Table 2. — *Expression of ESA immunoreactivity in CGIN cases.*

Case	Age (years)	ESA	
		Baso	Cyto
1	34	+	–
2	50	+	+
3	45	+	+
4	38	+	+
5	33	+	–
6	47	+	+
7	42	+	+
8	38	+	+
9	41	+	+
10	51	+	–
11	46	+	+
12	37	+	+
13	39	+	+
14	43	+	+
15	41	+	+

Table 3. — *Expression of ESA immunoreactivity in cases of in situ adenocarcinoma.*

Case	Age (years)	ESA	
		Baso	Cyto
1	55	+	+
2	42	+	-
3	33	+	+
4	37	+	+
5	45	+	+
6	36	+	+
7	40	+	+
8	49	+	+

Table 4. — *Expression of ESA immunoreactivity in cases of invasive adenocarcinoma.*

Case	Age (years)	ESA	
		Baso	Cyto
1	35	+	+
2	42	+	+
3	46	+	+
4	48	+	+
5	52	+	+
6	32	+	+
7	36	+	+
8	47	+	+
9	55	+	+
10	49	+	+
11	31	+	+
12	43	+	+
13	44	+	+
14	38	+	+
15	45	+	+
16	51	+	+
17	40	+	+

Discussion

Over the last two decades there has been an intense research interest in studies of glandular lesions, which has dramatically increased our knowledge in these areas. The pathologists became more familiar with these lesions and with various other entities which may be mistaken for cervical adenocarcinoma and AIS [8]. In 1952 an early example was provided by Helper *et al.* who described dysplastic endocervical glands next to invasive adenocarcinoma [9]. In 1957 Stewart in his studies on cervical adenocarcinoma and its precursor lesions, observed that cases of AIS progressed to invasive adenocarcinoma [10].

Cervical glandular intraepithelial neoplasia (CGIN) is histologically defined as any glandular dysplasia that is less severe than AIS [11, 12]. According to Jaworski in CGIN we find nuclear enlargement and hyperplasia, slight nuclear pseudostratification and finely granular chromatin. Additionally there is evidence of cellular proliferation and turnover with mitosis and apoptotic bodies rarely seen. Most of the glands had an abnormal profile with irregular branching and building. Intraluminal tufts and low papillary projections lacking stromal cores were also observed [13].

In this project the immunohistochemical expression of ESA in CGIN and adenocarcinomas was studied and evaluated. The findings were correlated with normal endocervical epithelium. ESA is identified from the monoclonal antibody VU1D9, which is derived from the small cell lung carcinoma cell line H69. VU1D9 recognizes a 40-KDa cell surface glycoprotein and strongly labels both normal epithelial cells and carcinomas [7]. ESA shows positivity in normal skin and skin tumors as well as in sebaceous and apocrine carcinomas. It has been reported to be localized to the basolateral membrane and to a lesser degree to the cytoplasm in normal skin.

In this project ESA was positive in normal endocervical cells and was restricted to the basolateral membrane as in the skin appendage [7]. We must also emphasize that ESA staining was positive in most of the CGIN cases and extended to the diffuse cytoplasmic membrane in a manner similar to most of the endocervical adenocarcinoma specimens. These observations suggest that there was a distinct difference between normal endocervical cells and tumor cells including endocervical dysplasia.

The present study shows that ESA expression is generally considered to be an early event in endocervical malignancies, supporting the concept that CGIN may be a precursor lesion to cervical adenocarcinoma.

Fig. 1

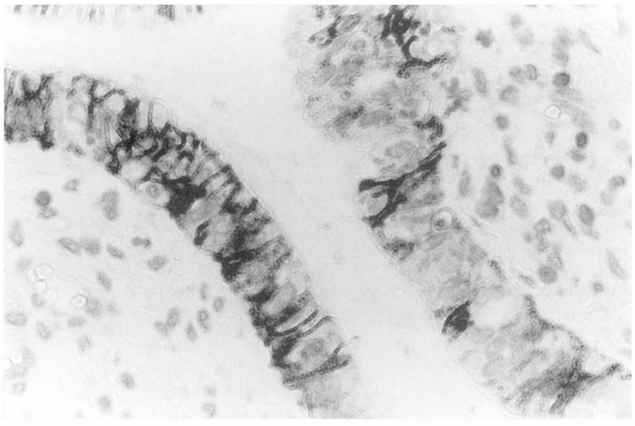

Fig. 2

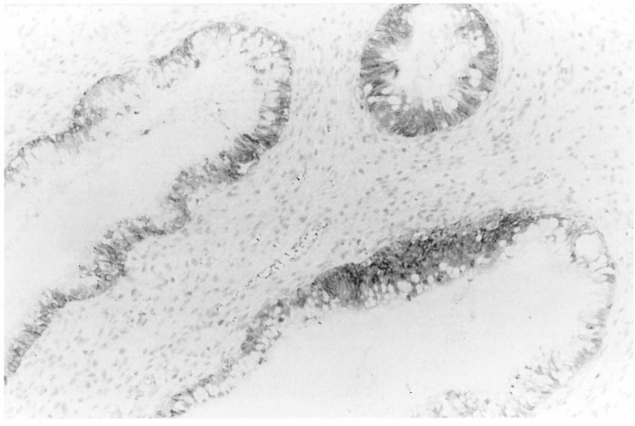

Fig. 3

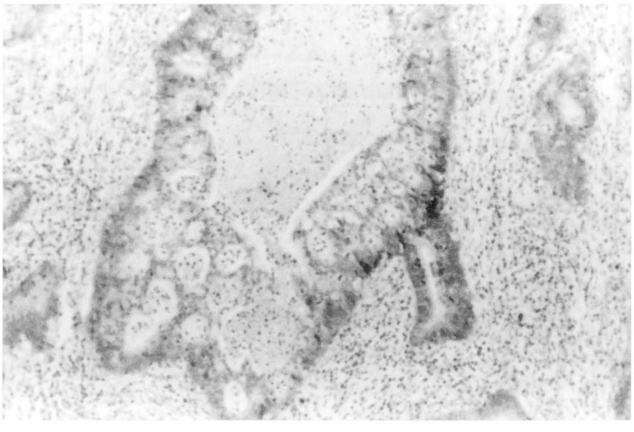

Figure 1. — Localization of ESA in the basolateral membrane of a normal endocervix (x 100).

Figure 2. — Localization of ESA in endocervical glandular dysplasia in the basolateral and cytoplasmic membranes (x 10).

Figure 3. — Localization of ESA in invasive adenocarcinoma. ESA immunoreactivity was found in the cytoplasm of cancer cells (x 10).

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