

Invasive adenocarcinoma of mixed endocervical and clear cell type, associated with invasive squamous cell carcinoma of the cervix uteri. A case report

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Summary

A case of invasive adenocarcinoma (predominantly of endocervical type but also with clear cell elements blended in part of the growth) associated with squamous cell carcinoma of the uterine cervix is reported in a young woman aged 18 years. Malignant squamous and atypical glandular cells were detected in Papanicolaou (Pap) smears, which raised the question of a mixed tumor. A diagnosis of cervical cancer was justified by means of a punch biopsy and the patient was treated by modified radical hysterectomy. Histologic and immunohistochemical examination of the hysterectomy specimen revealed two distinct types of an invasive malignant tumor, i.e., of glandular and squamous cell origin, closely related but not integrated. Interestingly, the glandular component comprised both endocervical and clear cell elements.

Careful consideration of squamous or glandular atypia in cytological smears may lead to a more precise diagnosis, especially in young women.

Key words: Collision tumors; Mixed adenocarcinoma; Squamous cell carcinoma; Uterine cervix; Young patients.

Introduction

Several combinations of in situ and invasive cervical carcinoma of both glandular and squamous origin have been reported in coexistence in the literature [1, 2]. Usually located adjacent to each other and, at times, intermingling, these lesions probably originate from the subcolumnar reserve cells of the transformation zone [1].

Pura *et al.* [3], in a 43-year period, described only five collision tumors of the cervix. The concomitant occurrence of adenocarcinoma and noninvasive squamous neoplasia has been reported only sporadically [4, 5]. In a series of 159 primary adenocarcinomas of the cervix, there were nine cases (6%) of coexistent cervical squamous intraepithelial neoplasia. Curiously, the coexistence of squamous carcinoma in situ and adenocarcinoma in situ has been repeatedly observed [4]. However, reports of invasive forms of squamous carcinoma and adenocarcinoma of the uterine cervix are very rare and rather isolated [4, 5].

Clear cell adenocarcinoma of the cervix, though increasing in younger age groups, remains a rare tumor [6, 7]. Howard *et al.* [8], in a 14-year period report, detected only three cases.

The average age of patients with invasive squamous carcinoma of the cervix is 53 years, while the respective age for adenocarcinoma and clear cell carcinoma is 49 and 19 years [9].

We report a case of invasive cervical adenocarcinoma of mixed endocervical and clear cell type associated with

a squamous cell carcinoma (collision tumor) in an 18-year-old woman. Specifically, we present the cytologic, histologic and immunohistochemical diagnostic profile of the young patient and we discuss certain differential diagnostic aspects.

Case Report

An 18-year-old woman was referred to our outpatient department because of vaginal discharge and postcoital bleeding. The patient was of low socioeconomic class and early age at first intercourse, and had multiple sexual partners. She was nulliparous, free of pathology in her case history and her mother had not been exposed to diethylstilbestrol. The gynecologic examination revealed an exophytic mass protruding from the endocervix into the vagina. A Pap smear was taken which showed malignant squamous cells and atypical cells of both squamous and glandular epithelial origin. Biopsy of the exophytic mass revealed a cervical cancer composed of both squamous and glandular components. The patient underwent a Wertheim hysterectomy with bilateral pelvic lymphadenectomy. Parametria and adnexa were tumor free. Histologic examination of the hysterectomy specimen demonstrated an invasive adenocarcinoma (predominantly of endocervical type with clear cells blended in part of the growth) associated with an invasive squamous cell carcinoma of the cervix. Tumor extension to pelvic lymph nodes, veins, and nerves was not found. The patient has been followed for 96 months, with no evidence of recurrent disease.

Materials and Methods

Pap smears were taken from the vaginal vault, the vaginal aspect of the cervix and the endocervical canal. The technique

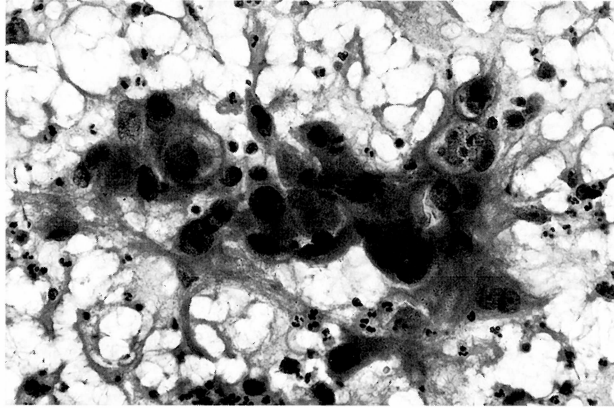


Fig. 1

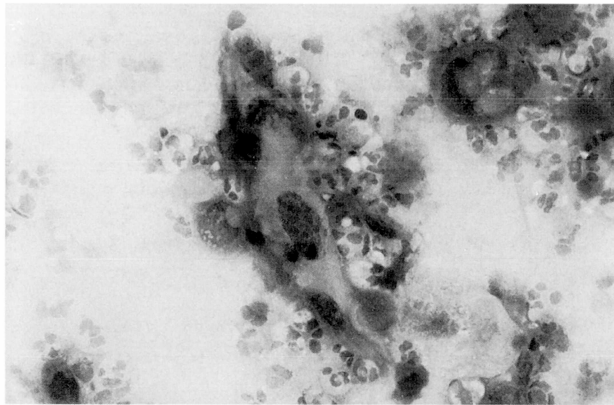


Fig. 2

Figure 1. — Papillary-like grouping. The cytoplasm contains large vacuoles enclosing granulocytes. The nucleus is displaced. (Papanicolaou stain X 400).

Figure 2. — Tadpole cell. The cytoplasm is yellowish coloured. The elongated spindle-shaped nucleus closely follows the shape of the cytoplasm. (Papanicolaou stain X 400).

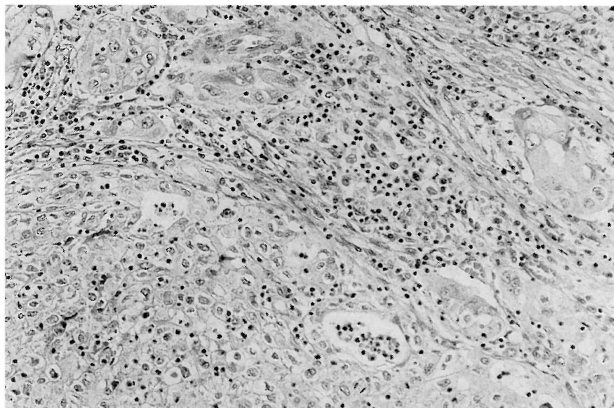


Figure 5. — Carcinoma of the cervix uteri with adenomatous and clear cell elements. (H & E X 200).

used was a cervical scrape obtained with a plastic pap-perfect spatula under direct vision with the vaginal speculum in position. The rounded end of the spatula was used to sample the vaginal vault. Medscand's cytobrush was used to provide an adequate and representative specimen from the endocervical canal and the squamocolumnar junction [10]. The smear was first cytospray-fixed and subsequently stained with the Papanicolaou

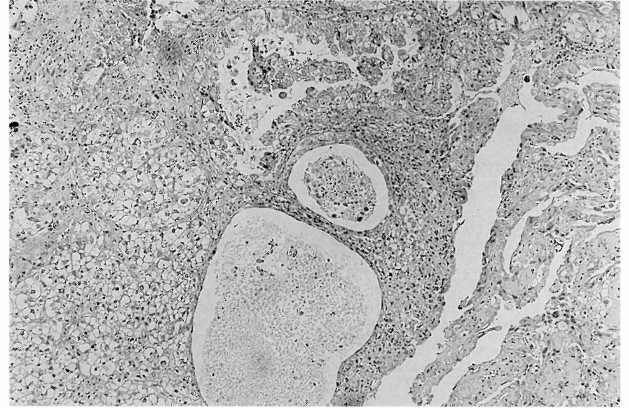


Fig.

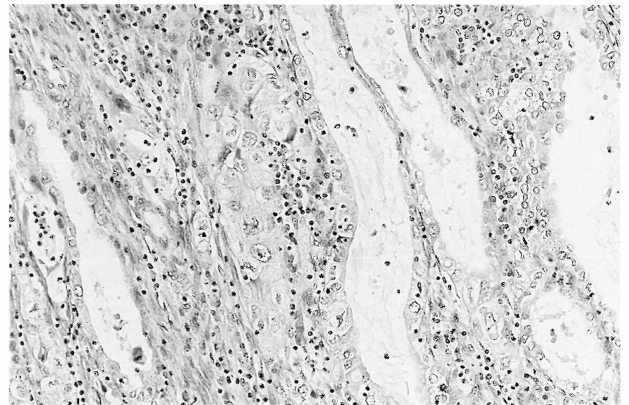


Fig.

Figure 3. — Carcinoma of the cervix uteri showing mixed squamous cell and adenomatous elements. (H&E X 400).

Figure 4. — Carcinoma of the cervix uteri showing mixed squamous cell and clear cell elements. (H&E X 400).

technique. A punch biopsy was performed on the macroscopically detected lesion. The tissue was fixed in 10% formal saline for 24 hours and embedded in paraffin wax. For histologic study, paraffin blocks from both the biopsy sample and the Wertheim's specimen were cut in 5 μ m thick sections and stained with hematoxylin and eosin. Immunohistochemical staining was performed using the Avidin Biotin peroxidase Complex (ABC) method to detect the expression of high molecular weight keratin (DAKO) and epithelial membrane antigen (EMA).

Cytologic Findings

The endocervical smear was rich in epithelial cells, scattered in groups, against a background of neutrophils, erythrocytes, and debris. There were a number of epithelial cells showing anisonucleosis, hyperchromasia, and granular, clumped chromatin. The abnormal nuclei contained several irregular nucleoli of varying size. The cytoplasm of certain cells was filled with vacuoles displacing the nucleus at the periphery. These cytologic features gave the impression of atypical cells of the AGUS rather than the t ASCUS category, according to the criteria defined in the Bethesda system (Figure 1).

In some areas of the smear, small to medium size atypical cells with cytologic features of mild dyskaryosis were also seen. This raised the question of a coexistent squamous intraepithelial lesion (SIL).

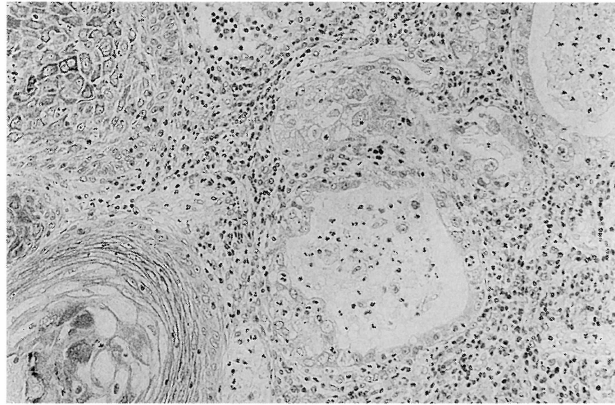


Fig. 6



Fig. 7

Figure 6. — Epithelial membrane antigen (EMA) expression by both adenomatous and squamous cell elements in a carcinoma of the cervix uteri. (X 400).

Figure 7. — Cyokeratin expression by squamous cell elements in carcinoma of the cervix uteri. Note that the adenomatous elements are negative. (X 200).

There were a number of cells with features typical of a highly-differentiated squamous cell carcinoma (Figure 2).

The cytology report was positive for malignancy. Both possibilities of an AGUS and a squamous cell carcinoma were considered. The precise identification of the tumor's histologic type was not possible by means of the cytologic pattern. This led to a biopsy on the visible cervical lesion in order to establish the final diagnosis.

Histologic Findings

Histologic examination of the biopsy sample and the hysterectomy specimen showed an invasive neoplasm, which consisted of a mixture of adenocarcinoma and squamous cell carcinoma. The predominant element of the tumor, however, was the adenomatous one and was formed of endocervical and clear cell type components (Figure 3). The malignant glands were lined by a mucus secretory epithelium of moderate differentiation. The clear cell component was of a solid growth pattern, with cells containing glycogen but not mucin. Mitoses were not frequent.

The squamous cell carcinoma of the cervix was moderately-differentiated of the large cell non-keratinizing type (Figure 4). Inter-cellular bridges were seen, as were cytoplasmic keratinization and keratohyaline granules. The nuclei were large and hyperchromatic. Mitotic figures were uncommon. There was an intense inflammatory response, consisting mainly of poly-

morphonuclear leukocytes and lymphocytes (Figure 5). The tumor arose from the squamocolumnar junction and infiltrated almost 1/2 of the cervical tissue.

Immunohistochemical Findings

Immunohistochemical staining showed a strong reactivity of malignant glandular elements with epithelial membrane antigens (EMA) (Figure 6) and an equally strong reaction of malignant squamous cells with keratin (Figure 7).

Discussion

In this case the cervix contained two distinct tumors, first an *invasive* squamous cell carcinoma originating from the squamocolumnar junction, and secondly an *invasive* adenocarcinoma with mixed endocervical and clear cell elements. The coexistence of invasive squamous and glandular elements in a carcinoma of the uterine cervix is a rather rare condition. Maier *et al.* [4] in a review of 389 invasive cervical adenocarcinomas reported only three cases. Moreover, the participation of a clear cell component in the malignant cervical tumor makes the case exceptional. Clear cell carcinomas represent only 1.5%-3% of all cervical cancers [5, 11, 12]. Goodman *et al.* [8] reported only three patients with clear cell adenocarcinoma detected in a study period extending over 15 years. Clear cell adenocarcinoma is considered a tumor of poor prognosis, apparently because of early lymph node involvement [13]. The prospects are more ominous in women less than 19 years of age [14]. Invasive cervical cancer is very uncommon in the first two decades of life. Maddux *et al.* [15] in a study extending over a period of 18 years, found 40 women aged 25 years or less (range 20.7-25.9 years) with invasive cancer and none under 20 years of age. Young age is an independent poor prognostic factor for cervical cancer [16], while mixed adenocarcinomas have a more unfavorable prognosis than pure ones of comparable stage [17]. Despite this gloomy outlook, the young patient reported in our study has exceeded a 5-year disease-free survival without any evidence of recurrent disease.

Horowitz *et al.* [18] suggested that patients with squamous cell carcinoma and adenocarcinoma could represent two distinct populations with different risk factors. In their series, patients with adenocarcinoma appeared to be of a more affluent socioeconomic background with significantly better education and greater income.

The patients had less relation with early age at first intercourse and smoking. Brand *et al.* [19] confirmed that there are, as yet, no recognized etiologic factors for cervical adenocarcinoma and no relation has been established with age at first intercourse, sexual activity, or smoking. The young woman in our report presented an epidemiologic profile similar to that of a squamous cell cancer, even though the adenomatous element predominated in the growth pattern.

The cytologic manifestations of squamous cell carcinoma are easy to interpret. The term "atypical endocervical cells of undetermined significance" includes cytolo-

gic manifestations of a number of qualifying lesions to indicate whether a reactive or a premalignant/malignant process is represented. The smear in our case was cellular and composed, mostly, of individual abnormal cells, small to medium in size. The cytoplasm was vacuolated, or dense and cyanophilic. In the former (vacuolated cells), the nucleus was peripherally pushed, the chromatin was moderately to coarsely granular and evenly dispersed, giving the nuclei a dark, hyperchromatic appearance. Anisonucleosis and irregular nucleoli were observed. We considered that the atypical cells favored a diagnosis of AGUS in addition to squamous carcinoma.

Our evaluation of the cytologic smears reaffirms the results of previous studies regarding the lack of reliable criteria in distinguishing squamous from glandular neoplasia of the cervix [9, 20]. It is, therefore, important that cytopathologists should bear in mind the possibility of a mixed cancer on the same cervix, especially in young women. Careful consideration of cervical smears and proper interpretation of atypical squamous or glandular lesions could eliminate the misdiagnosis of such interesting cases.

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