

ADENOID CYSTIC CARCINOMA OF THE UTERINE CERVIX

Report of six cases and review of the literature

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SUMMARY

Six cases of adenoid cystic carcinoma of the cervix were reported. Five of them were found among 1500 cervical biopsies. This frequency indicates that this tumor is more frequent than stated in the literature. In all cases the clinical data, colposcopic, cytological and histopathological findings, as well as the type of treatment and follow-up were reported. The paper points out that the cytology and colposcopy have characteristic features for the diagnosis. Because of the rarity of the tumor, the prognostic approach is not easily defined. The cases considered as stage II and III have poor prognosis, developing pulmonary metastasis as seen in one of our patients.

INTRODUCTION

Adenoid cystic carcinoma (A.C.C.) of the uterine cervix is a rare type of uterine malignancy that afflicts postmenopausal women. It also occurs in the major and minor salivary glands, in the tracheo-bronchial tree, in the breast and vulva (Ashley, 1978). A.C.C. has a characteristic histologic pattern, regardless of its anatomic localization. It is composed of basaloid cells arranged in nests, cords, or sheets and forms an adenoid-cystic pattern.

We have found only 41 reported cases of A.C.C. of the uterine cervix (Paalman and Counseller 1949, Moss and Collins 1964, Mc Gee et al 1965, Baggish and Woodruff 1966, Dahlin 1966, Grafton et al 1968, Cabanne et al 1969, Benitez et al 1969, Gallagher et al 1971, Baggish and Woodruff 1971, Miles and Norris 1971, Van Valden and Chuang 1972, Maza et al 1972, Gordon et al 1972, Ryden et al 1974, Genton 1974, Russel and Lavery 1975, Hurt et al 1977). Cytological smears had been performed in 25 of these reported cases. The results were classified as *negative*, *suspicious* or *positive*, but the cytological features were not described. In 1975, one of us (Bittencourt) presented at the *VI Congresso Brasileiro de Citologia* the cytopathological features of this tumor: the evidence presented suggested that cytology could be diagnostic of this entity. One year later, Grafton et al (1976) described the cytological pattern of three cases. These authors believed that when the acinar pattern was present, A.C.C. might be suspected.

This paper reports six additional cases of A.C.C. In all cases the clinical data, the colposcopic, cytological and pathological findings, the treatment and the follow-up are considered.

MATERIAL AND METHODS

Five of the six A.C.C. cases here described were found among 1,500 cervical biopsies performed at a gynecologic cancer prevention clinic, in Salvador, State of Bahia. The other cases were sent to us from a private pathological laboratory, in Salvador. All the six patients had cytologic smears. The smears were fixed in 95 per cent alcohol and stained by Papanicolaou method. The criteria for cytological study included cellular morphology and arrangement, and frequency of adenoid pattern.

In five cases, colposcopic examination was performed. The clinical stage was made according to the Clinical Classification of Carcinoma of the Cervix of the International Federation of Gynecology and Obstetrics (FIGO). The therapeutic criteria were established depending on the clinical stage and the age of the patients. In cases 1, 2 and 6, with age greater than 70 years, and in case 3, with stage III B, therapy consisted of radiation (telecobalt therapy and vaginal radium moldage). Two of these patients underwent only telecobalt therapy, because of a narrowing of the vaginal canal (See Table 1). Cases 3 and 4, 60 and 65 years old, respectively, (Stage I B) were submitted to radical hysterectomy (Wertheim). The microscopic examination of the surgical specimen in case 5 revealed local infiltration of parametrium and vagina and metastasis to pelvic lymph nodes. For this reason, complementary treatment with telecobalt therapy was used. Follow-up study included gynecologic examination, vaginal smears and chest roentgenogram. The original microscopic sections were reviewed, and new histologic sections were stained with Alcian blue and periodic-acid Schiff reagent with and without diastase.

RESULTS

Clinical findings—The patients ranged in age from 56 to 75 years at the time of diagnosis, with an average age of 66 years. All the patients were multiparous and postmenopausal. The initial complaint was bloody vaginal discharge of few days to one year of duration. Four patients were black and two were white. Colposcopic examination in cases 1, 2, 3 and 4 revealed a mass, the surface of which consisted of many small confluent pearly vesicle-like formations with fine vascularization. In case 5 the cervix was replaced by a friable mass with a colposcopic aspect suggestive of invasive squamous cell carcinoma (I.S.C.C.). The follow-up of the patients can be seen in Table 1.

Cytological findings—In all smears many clusters of cells with scant cytoplasm and frequent overlapping were seen. These clusters showed adenoid pattern (Figs. 1 and 2) and imitated the masses of basaloid cells seen in the histologic sections. The case number 6 was the most differentiated. The cells showed slight variation in nuclear size. The nuclei were round or oval and had finely granular chromatin and no nucleolus. In this case the adenoid pattern was very frequent (Figs. 1 and 2). In the other five cases the cells showed oval or round hyperchromatic nuclei with moderate to marked variation in nuclear size. Adenoid pattern was seen in few clusters (Figs. 3 and 4). In all cases, among the tumor cells, rare cells with slightly larger nucleus, with finely granular chromatin and sometimes with an inconspicuous nucleolus were seen (Fig. 4). Mitosis were observed in only two cases. Squamous malignant cells were not present in the two cases associated with I.S.C.C. The background of the smears was bloody.

Gross findings—In case 4 the pathological study of the surgical specimen revealed a localized lesion $3.5 \times 2.5 \times 2$ cm. In case 5, it was seen a huge tumor

Table 1

Reported Cases of Adenoid Cystic Carcinoma of Cervix

N.º	AGE (years)	CLINICAL STAGE	ASSOCIATED I.S.C.C.	TREATMENT	FOLLOW-UP (yr)
1	73	II B	—	TeCo (6,000 rad)	Dead (cause unknown) 1.4y
2	75	II B	—	TeCo (5,000 rad)	Living with pulmonary metastases 4.10y
3	56	III B	—	TeCo (7,000 rad) VRM (4,000 rad)	Living and well 1.1y
4	65	I B	—	R.H.	Living and well 0.9y
5	60	I B	+	R.H. TeCo (5,000 rad)	Living and well 0.9y
6	72	I B	+	TeCo (3,000 rad) VRM (8,000 rad)	Living and well 2.3y

LEGENDS: I.S.C.C. — Invasive squamous cell carcinoma

TeCo — Telecobalt therapy

VRM — Vaginal Radium/moldage

RH — Radical hysterectomy

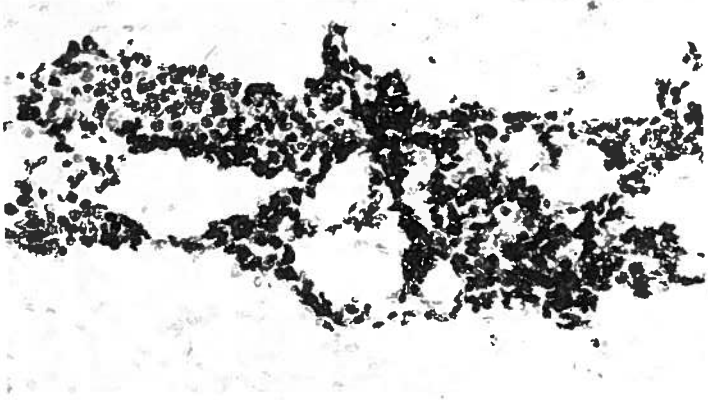


Fig. 1—Cervical smear from case 6. Note the characteristic adenoid pattern and the overlapping of cells. Papanicolaou $\times 100$.

Fig. 2—Another view from case 6. The cells show slight variation in nuclear size and round spaces among them, configurating an adenoid pattern

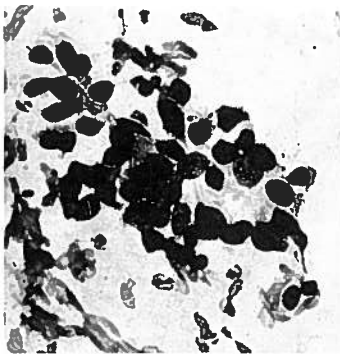
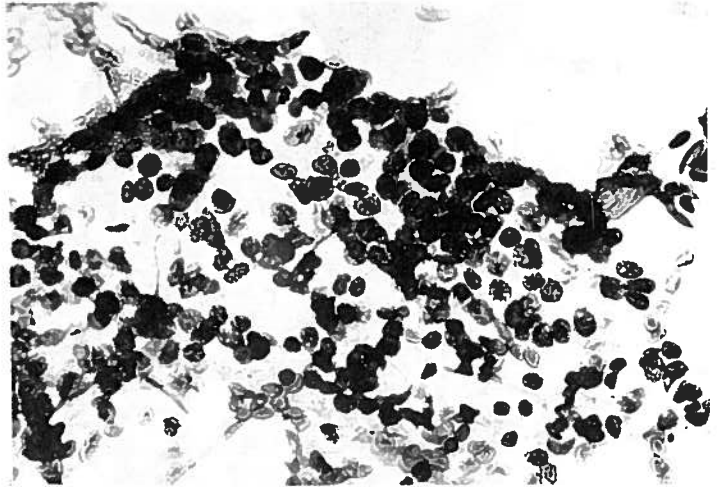


Fig. 3—Cervical smear from case 5. A cluster of cells with hyperchromatic nuclei and marked variation in nuclear size. At right the cells show an adenoid structure. Papanicolaou $\times 400$

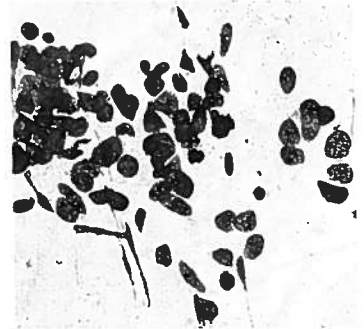


Fig. 4—Cervical smear from case 2. A cluster of cells with hyperchromatic nuclei showing, at right, a few nuclei with granular chromatin and inconspicuous nucleolus. Papanicolaou $\times 400$

7×5×3 cm, with extension to the upper third of the vagina, parametrium and pelvic lymph nodes. The pelvic lymph nodes of this case were involved by metastatic carcinoma with squamous cell features. The cut surface of both surgical specimens disclosed a whitish brilliant granular appearance.

Histopathological findings—The characteristic cell of A.C.C. has an oval or round nucleus and little cytoplasm and is arranged in solid nests and cords. The peripheral layer of the solid masses of cells often showed palisade arrangement of the nuclei. These solid areas were seen intermingled with characteristic adenoid structures (Fig. 5, 6) and less frequently with cysts partially filled with eosinophilic amorphous material that is PAS positive, diastase resistant, and alcian blue positive. The epithelial components were separated by a myxomatous stroma that also stains with Alcian blue and PAS. In one case, in many areas, neoplastic cells were seen isolated within the myxomatous stroma (Fig. 7). In case number 6 the cells showed slight variation in nuclear size and fine chromatin. The adenoid pattern was very frequent. In the other cases the cells showed moderate to marked variation in the nuclear size and, in case number 4, bizarre giant nuclei (Fig. 7). The adenoid pattern was less frequent in these cases. Sometimes, the nuclear pleomorphism varied in different areas of the same tumor (Fig. 7).

In two cases there was association with I.S.C.C. (Table 1). In these cases, it was possible to see transitional forms between the anaplastic basaloid cells and the anaplastic squamous cells. In case 2 areas of benign squamous differentiation were seen within the masses of basal cells.

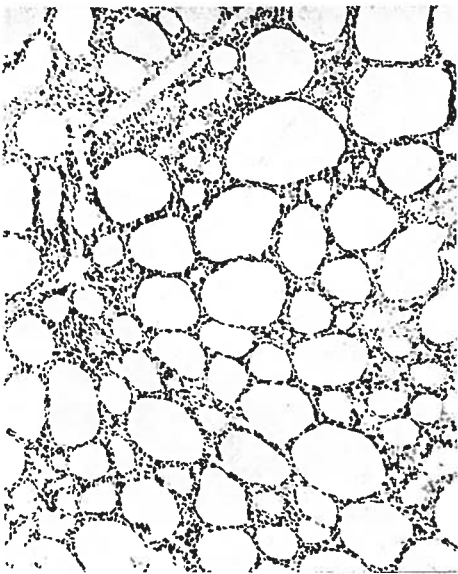


Fig. 5 — Case 6. (Typical adenoid pattern (HEX100))

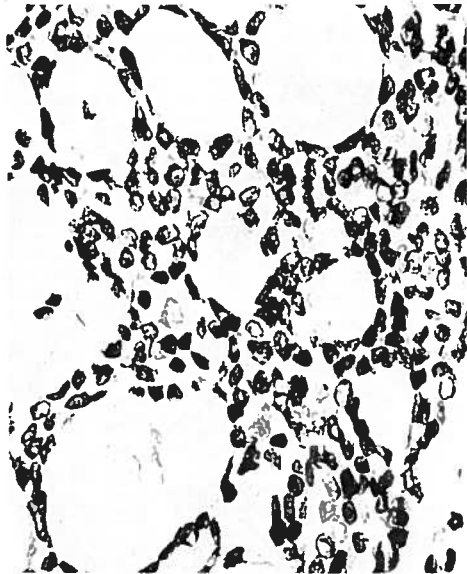


Fig. 5 — Case 6. A higher magnification. See the neoplastic cells with scant cytoplasm and small nuclei. There is slight variation in the nuclear size HEX400

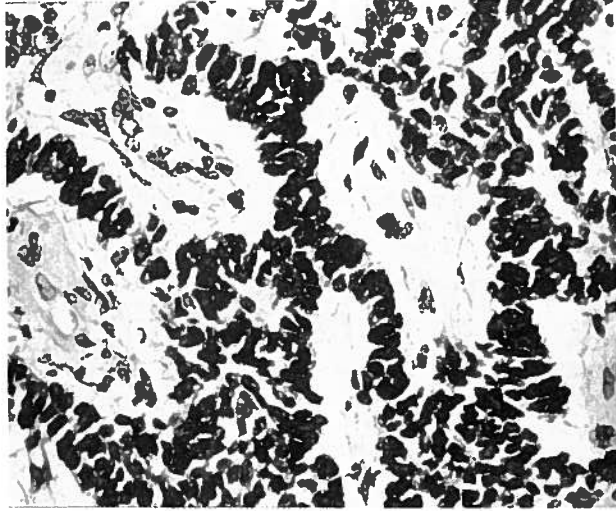


Fig. 6 — Case 2. Adenoid pattern. In the spaces among the neoplastic cells we can see a myxomatous stroma. The cells show hyperchromatic nuclei with moderate variation in size
HE \times 400

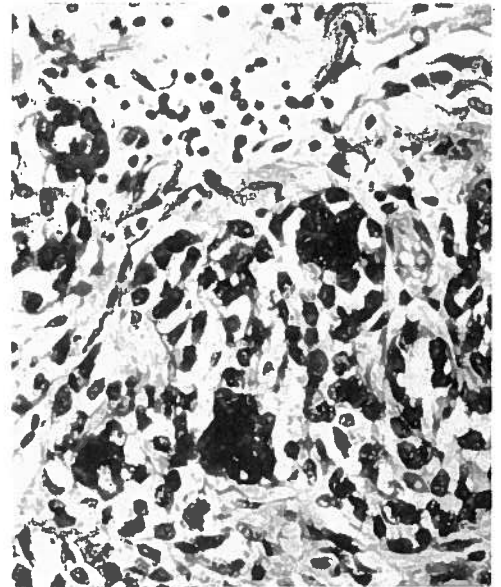
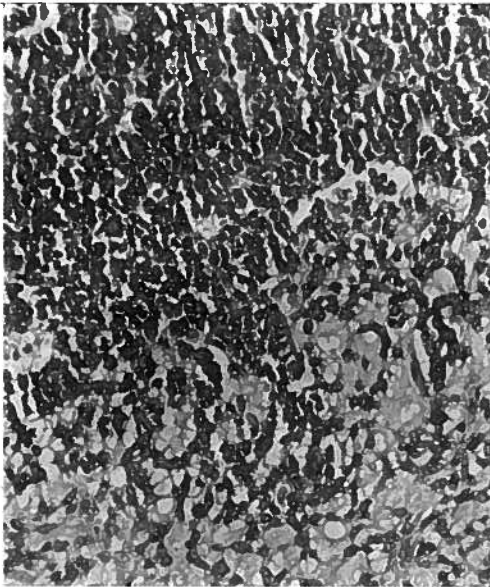


Fig. 7 — Case 4. At left, cells with small nuclei dissociated within myxomatous stroma HE \times 200.
At right, in another field, we can see bizarre giant nuclei HE \times 400

DISCUSSION

The fact that five of six cases here reported was found among 1,500 cervical biopsies suggests that this tumor may be a more frequent cervical neoplasm than the scarcity of reports indicates.

Like the cases in the literature, our patients had an average age of 66 years (Miles et Norris 1971). In four patients colposcopic examination disclosed a soft tumor covered by multiple confluent, small, pearly, vesicle-like structures. We believe that this colposcopic pattern may be characteristic of the A.C.C. since this aspect has not been described in any other cervical neoplasm (Cramer 1964, Salgado et al 1970, Mestwerdt and Wespi 1974).

The cytologic diagnosis of A.C.C. should be based on the presence of cells with scant cytoplasm arranged in clusters of different sizes and forms, with frequent cellular overlapping but without three dimensional configuration. The presence of round spaces between the malignant cells gives the clusters a characteristic adenoid pattern.

The cytological differential diagnosis should be made with endometrial adenocarcinoma, which cells also shed in clusters, but frequently with three dimensional configuration and without adenoid pattern. Endometrial adenocarcinoma cells have usually an eccentric vesicular nucleus, prominent nucleolus and a vacuolated cytoplasm. (Riotton and Christopherson 1973, Schneider and Staemmler 1977), whereas A.C.C. cells have a non-vacuolated, scantier cytoplasm and a hyperchromatic nucleus without nucleolus. The differential diagnosis should also be made with endocervical adenocarcinoma that also sheds clusters of cells. Adenocarcinoma cells are larger, with abundant, vacuolated cytoplasm, vesicular nucleus and prominent or multiple nucleoli. In addition, in endocervical adenocarcinoma single cylindrical tumor cells and side-to-side arrangements may be seen (Riotton and Christopherson 1973, Schneider and Staemmler 1977).

We believe that considering all the characteristics above mentioned, mainly the presence of an adenoid pattern and the absence of conspicuous nucleoli, it is possible to give an accurate cytologic diagnosis of A.C.C.

Histologically, the following aspects were seen

- 1 — Basaloid cells with indistinct cytoplasm arranged in nests and cords
- 2 — Adenoid pattern
- 3 — Myxomatous stroma

The frequency of these different aspects varied from case to case. In order to detect the presence of these aspects, in two instances we had to perform more than one biopsy. Sometimes, A.C.C. presents a marked pleomorphism with giant malignant cells as seen in our case (Fig. 7) and in two reported cases (Van Velden and Chuang 1972, Gordon et al 1972). In two cases, A.C.C. was associated with I.S.C.C. Such an association was reported in six cases in the literature (Moss and Collins 1964, Baggish and Woodruff 1971, Gordon et al 1972).

In their ultrastructural studies, Koss et al (1970) showed that the spaces seen in A.C.C. were not duct or glandular spaces but extracellular compartments enclosed by tumoral cells and lined by an uninterrupted basement membrane. As other authors (Gordon et al 1972) have emphasized, we found that the content of these spaces and the mixomatous stroma gave the same staining reaction with PAS and Alcian blue stain. Therefore the A.C.C. should not be considered to be an adenocarcinoma as has been previously suggested (Miles et Norris 1971, Hurt et al 1977).

The published reports do not give sufficient data for an evaluation of the biological behaviour of the A.C.C. Only 18 patients had follow-up intervals greater than three years and in half of these cases, the clinical stage was not stated. Among the nine staged

Table 2
Literature cases with follow-up interval greater than 3 years

AUTHORS	FOLLOW-UP (years)	STATUS	TREATMENT	CLINICAL STAGE	ASSOCIATED I.S.C.C.
1 Baggish and Woodruff 1966, 1971	13	Well	H	...	—
2 » » »	7	»	H	...	—
3 » » »	5	»	H	...	—
4 Grafton et al	3.6	Dead with tumor	R	...	—
5 » » »	5.8	Recurrence	H	...	—
6 Gallager et al (case 2)	4	Dead with tumor	R	...	—
7 » » » (case 3)	3.3	Dead, other disease	R	...	—
8 Maza et al	3	Recurrence	R	...	—
9 Dahlin et al	4	Recurrence	R	...	—
10 Gordon et al	4	Recurrence	R	II	—
11 Baggish and Woodruff 1971 (case 5)	10	Dead with tumor	R	II B	+
12 Hurt et al	5	Not stated	Not stated	II	—
13 Miles and Norris (case 5)	4	Well	R	I	...
14 » » » (case 6)	5.2	Well	R	I	...
15 » » » (case 8)	3.3	Recurrence	H + R	II	...
16 » » » (case 9)	5.3	Recurrence	H	I	...
17 » » » (case 11)	3	Dead with tumor	H + R	I	...
18 » » » (case 12)	3.3	Dead with tumor	R	I	...

LEGENDS: H — Hysterectomy

R — Radiation

I.S.C.C. — Invasive squamous cell carcinoma

cases only two can be considered to be unassociated with I.S.C.C. (see Table 2). These two patients (Stage II) were living four and five years, respectively, after treatment. One of them had local recurrence of the tumor (Gordon et al 1972, Hurt et al 1977). On the other hand, only one of our cases had longer follow-up (Case 2). This case (Stage II B) treated by telecobalt therapy developed pulmonary metastasis four years after treatment.

In table 2 we can see five instances of favorable prognosis of patients with A.C.C. These patients are living and well 4-13 years after diagnosis. Two of these patients had stage I and were treated with radiation therapy. In contrast, A.C.C. in its pure form, when in stages II and III, may have an unfavorable prognosis, developing pulmonary metastasis in spite of radiation therapy as occurred in our case 2 and in the patients of Ryden et al (1974) and Genton (1974).

The efficacy of the various modalities of therapy can not be adequately evaluated until more patients are reported with clinical staging and longer follow up. It must be emphasized that the histological differentiation of the tumor and a probable association with I.S.C.C. are factors that must be considered in the evaluation of the natural history of this tumor and choice of the best method of treatment.

RESUMO

São apresentados seis casos de carcinoma adenoide cístico do colo uterino, cinco dos quais foram observados de entre 1500 biópsias do colo uterino, indicando ser este tumor bem mais frequente do que indica a literatura. Em todos os casos foram considerados os aspectos clínicos, colposcópicos, citológicos, anátomo-patológicos, o tratamento e a evolução.

Os autores concluem que os aspectos citológicos e colposcópicos são característicos. Chamam a atenção para a dificuldade de se fazer uma avaliação prognóstica deste tumor devido a escassez de dados dos casos publicados. Mostram que os carcinomas adenoide císticos nos estádios II e III podem ter evolução desfavorável, desenvolvendo metástases pulmonares.

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