Primary signet-ring cell carcinoma of the uterine cervix with long term follow-up: case report

L. Insabato[1], S. Simonetti[1], R. De Cecio[1], S. Di Tuoro[1], G. Bifulco[2], A. Di Spiezio Sardo[2]

[1]Department of Biomorphologic and Functional Sciences, Pathology Section, [2]Department of Gynecology and Obstetrics, and Pathophysiology of Human Reproduction, University of Naples "Federico II", Naples (Italy)

Summary

Background: The uterine cervix represents an exceptional localization of signet-ring cell adenocarcinoma (SRCA). Most commonly, endocervical tumors with such morphology are metastatic from the breast or gastrointestinal tract while primary pure or almost pure tumors are extremely rare. No previous case of primary pure endocervical SRCA with follow-up longer than three years has been found in the literature. *Case report:* The present report describes such a case of a 46-year-old woman without evidence of recurrence eight years after the diagnosis. The patient was referred to the Gynecology Department for persistent abnormal vaginal bleeding of three months duration. Specular examination and colposcopy revealed a cervical polypoid lesion occupying the posterior lip of the cervix and protruding from the external uterine orifice. A biopsy of the lesion was interpreted by the pathologist as SRCA. An extensive search for an extrapelvic primary cancer was undertaken but revealed no evidence of malignancy. The patient underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic and paraaortic lymph node sampling for FIGO Stage 1B1 cervical cancer without any adjuvant chemo- or radiotherapy. The histological diagnosis showed neoplastic signet-ring cells confined in the head of the cervical polyps with minimal stromal infiltration. After surgery the patient underwent close follow-up including periodic cervicovaginal smears, bimanual vaginal examination, complete laboratory tests, ultrasound and abdominopelvic computed tomography. *Conclusions:* The prognostic relevance of primitive pure SRCA in the uterine cervix is unclear because of the relatively small number of cases. However the two early deaths out of six reported cases and the absence of follow-up longer than three years for the other affected patients, seem to suggest an aggressive behavior. The present case represents an exceptional long-term survival, probably related to an early diagnosis and a prominent polypoid growth of the neoplasia outside the uterus.

Key words: Follow-up; Signet ring cell carcinoma; Uterine cervix.

Introduction

Signet-ring cell carcinoma (SRCA) is a relatively rare neoplasm which principally arises in the stomach, colon-rectum, bladder and breast and which behaves as an aggressive and often lethal tumor [1].

The uterine cervix represents an exceptional localization of SRCAs. Most commonly, tumors with such morphology are metastatic from the breast or gastrointestinal tract [2-9], a condition which must be excluded before a primary cervical SRCA is diagnosed.

Primary pure or almost pure SRCAs of the uterine cervix are extremely rare [10-14] while more often they may be seen admixed with other more conventional subtypes of adenocarcinoma and adenosquamous carcinoma [15].

No previous case of primary pure endocervical SRCA with a long follow-up (> 3 years) has been reported in the literature. This report describes such a case in a 46-year-old patient without evidence of recurrence eight years after the diagnosis.

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Case Report

A 46-year-old multiparous (gravida 4, para 4) woman was referred to the Department of Obstetrics and Gynecology for persistent abnormal vaginal bleeding of three months duration.

Her past history was unremarkable for previous malignancy or significant medical conditions. She had never used oral contraceptives during reproductive age.

Specular examination and colposcopy revealed a cervical polypoid lesion occupying the posterior lip of the cervix and protruding from the external uterine orifice (EUO). A cervicovaginal smear revealed severe dysplasia according to the Bethesda classification and a biopsy of the lesion was interpreted by the pathologist as SRCA.

Bimanual vaginal examination was negative as both the cervix and the uterus were of normal size, shape and consistency and vaginal fornices and parametria were free of disease.

Transabdominal ultrasound scanning was negative for uterine and ovarian abnormalities.

An extensive search for an extrapelvic primary cancer was undertaken but abdominopelvic computed tomography (CT), mammography, cystoscopy, esophagogastroduodenoscopy and colonscopy revealed no evidence of malignancy.

The patient underwent a radical hysterectomy with bilateral salpingo-oophorectomy and pelvic and paraaortic lymph node sampling for FIGO Stage 1B1 cervical cancer. The patient provided written informed consent to perform the study.

The macroscopic appearance of the resected uterus is shown in Figure 1.

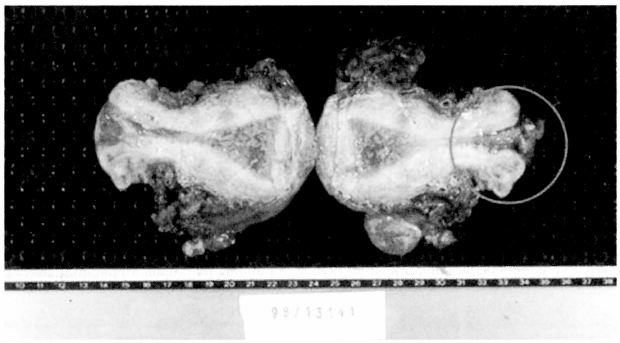


Figure 1. — Grossly the polypoid tumor on the posterior lip is seen (ring).

The cervix contained an 1.8 x 0.6 cm exophytic lesion arising from the posterior lip of its lower portion protruding from the EUO; no gross extension was noted to the isthmus, endometrium or vagina (Figure 1).

On histology, the bulk of the polypoid lesion was composed of infiltrating tumor cells with a signet-ring cell appearance without gland formations featuring a solid pattern (Figure 2a, b). Mitoses were seen; necrosis and vascular invasion were not observed. Periodic acid-Shiff (PAS) staining revealed PAS-positive diastase resistant introcytoplasmic material. The tumor cells infiltrated the stroma of the polyp, and peripherally normal glandular cervical epithelium was seen forward of the endocervical canal. Focally an adenocarcinoma in situ coexisted (Figure 3a, b).

For immunohistochemistry the following antibodies were used: cytocheratin 7 (CK7), DAKO, Glostrup, Denmark, 1:50 and cytocheratin 20 (CK20), DAKO, 1:50; microwaves were used for activation of epitopes. The tumor cells were negative for CK20 and strongly positive for CK7 (Figure 4).

Tumor metastases were not found in the lymph nodes. The uterus and ovaries were negative for tumor despite thorough sampling. The patient had a normal postoperative course and was discharged after seven days. After surgery the patient underwent close follow-up including periodic cervicovaginal smears, bimanual vaginal examination, complete laboratory tests, ultrasound and abdominopelvic CT. She was alive and without evidence of recurrence eight years after the operation.

Discussion

Hitherto only six cases [11-14] of primary pure or almost pure SRCA of the cervix have been reported in the literature.

The first case was described by Moll *et al.* more than 15 years ago. The case was a 50-year-old female who had been diagnosed with a SRCA protruding from the posterior cervical lip with metastasis involving the lymph nodes, ovary and bone. She underwent surgery plus pelvic irradiation but she died nearly ten months after the initial diagnosis [11].

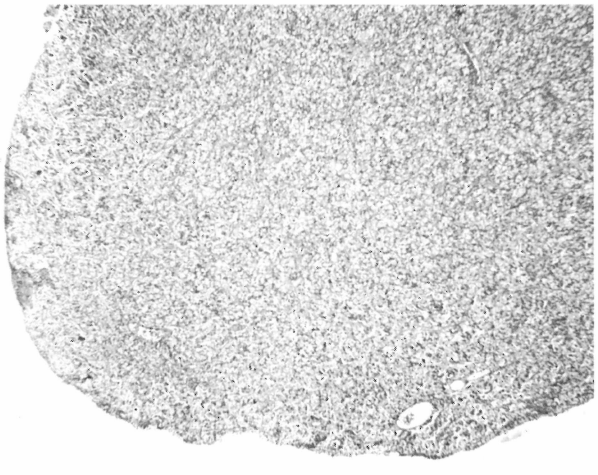
Haswani *et al.* [12] reported a short follow-up of two further cases occurring in young women (33 and 38 years), but in neitter of those patients was absolute proof of the absence of gastrointestinal tract tumor obtained. One patient died 18 months after the diagnosis of FIGO Stage IIIB SRCA treated with palliative radiotherapy and chemotherapy while the other one underwent surgery plus radiotherapy following a diagnosis of FIGO Stage IB SRCA and was free of disease nine months after radiotherapy.

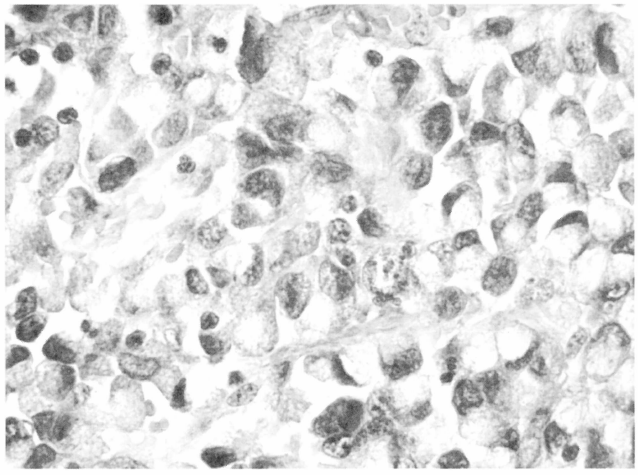
Mayorga *et al.* [13] described two other cases of FIGO Stage IB SRCA occurring in older patients (68 and 74 years). The patients had no evidence of recurrent or metastatic disease 35 and 25 months after radical hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection, respectively.

Cardosi *et al.* [14] described the first case of endocervical SRCA with neuroendocrine differentiation with a follow-up of six months without evidence of disease after primary therapy (surgery plus chemoradiation).

The present case reports the occurrence of a pure cervical SRCA with polypoid fashion in a 46-year-old female. A complete work-up of the patient was promptly performed to rule out a primary bladder, breast or gastrointestinal cancer. The tumor was in FIGO Stage IB1 and the patient underwent a radical hysterectomy with bilateral salpingo-oophorectomy and pelvic and paraaortic lymph node sampling without any adjuvant chemo- or radiotherapy.

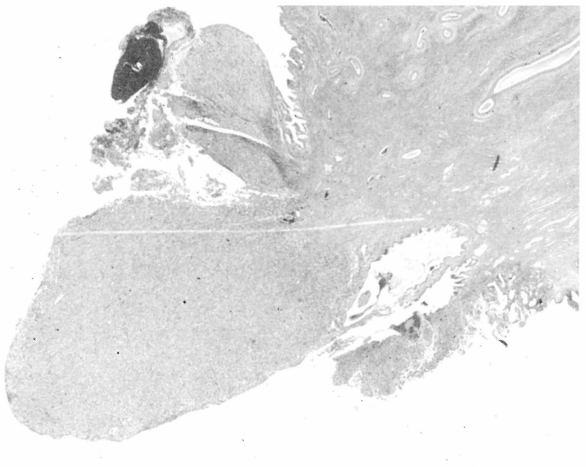
Fig. 2a





Fig

Figure 2a. — Solid pattern of the tumor without gland formation is seen on low power field.
Figure 2b. — Signet-ring cell appearance is evident.



. 3a

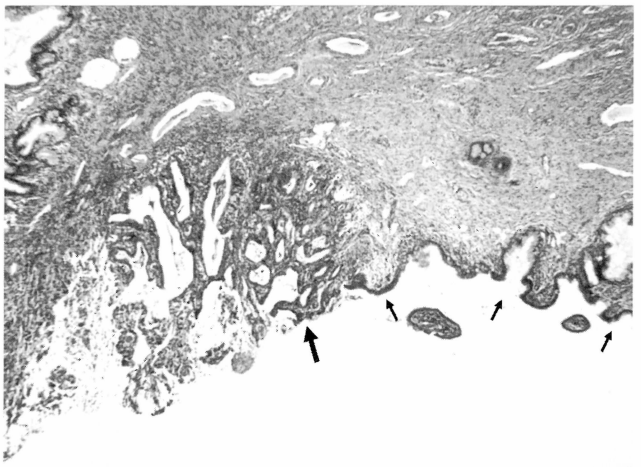


Fig. 3b

Figure 3a. — Whole-mount section showing a polypoid growth protruding from the external uterine orifice.
Figure 3b. — Adenocarcinoma in situ (large arrow) continuous with cervical columnar epithelium (small arrows).

This is the first case of primitive SRCA of the cervix with a long-term follow-up, as the patient had no evidence of recurrence eight years after the operation. We hypothesized that the excellent behavior of the present case depends on its unusual polypoid growth towards and through the EUO with no invasion of the endocervical stroma and endometrium.

Indeed, at microscopic examination, the neoplastic signet-ring cells were confined to the head of the cervical polyps with minimal stromal infiltration. Normal endocervical epithelium and an area of adenocarcinoma in situ next to the base of the polyp were seen.

The prognostic relevance of this morphology in the uterine cervix is unclear because of the relatively small number of cases [11-14].

However, in other sites SRCA usually presents a very poor prognosis because of an aggressive behavior and the diagnosis is usually made at advanced stages [1, 16-18].

The stomach is the most frequent site, but SRCA can arise in every site, also showing unusual localizations such as the pancreas, bladder or ovary [1, 19-21].

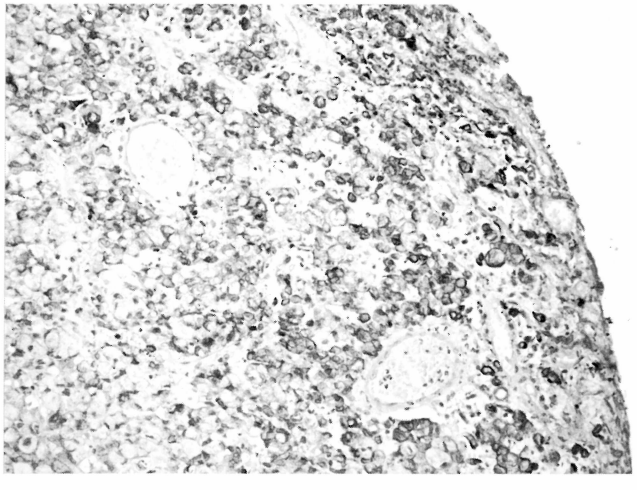


Figure 4. — Signet-ring cells showing an intense staining for CK7.

When cervical SRCA is diagnosed a great challenge is to differentiate the primary involvement from metastatic adenocarcinoma and endocervical involvement by SRCA of the endometrium. Most extragenital primary sites of SRCA metastatic to the cervix are the breast, stomach and large bowel [2-9]. Abdominal CT, magnetic resonance imaging (MRI), mammography, esophagogastroduodenoscopy and colonscopy allow the detection of these extra-uterine tumors. When a cervical metastastic form of extra-genital SRCA is diagnosed, a median survival of 12 months is expected [22]. Finally the differential diagnosis is as for some other exceptionally rare tumors like signet-ring cell non-Hodgkin lymphoma and signet-ring cell melanoma [13].

The presence of an area of adenocarcinoma in situ on histology might represent an early step in cancerogenesis of the uterine cervix. The presence of signet-ring cells in a cervicovaginal sample always needs an accurate interpretation without leading straightaway to a diagnosis of gastrointestinal or breast carcinoma metastasizing to the cervix [23, 24].

Fractionate dilatation and curettage (D&C) may be an useful tool to exclude an endometrial origin of the neoplasia, though this situation is extremely rare with only one report of primary SRCA of the endometrium with focal and microscopic cervical involvement [25].

In our case fractionate D&C was avoided as the endocervical origin of the polypoid lesion was evident at specular and colposcopic examination.

Conclusions

Every physician dealing with cervical pathologies should be aware of the possibility of a primary pure SRCA. A close cooperation between the pathologist, gynecologist and oncologist should be advocated to properly diagnose and treat such a rare condition.

The paucity of the reported cases makes any evaluation of the overall prognosis of this tumor difficult. However the two early deaths out of six reported cases and the

absence of follow-up longer than three years for the other affected patients, seem to suggest an aggressive behavior.

The present case represents an exceptionally long-term survival, probably related to an early diagnosis and a prominent polypoid growth of the neoplasia outside the uterus.

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Address reprint requests to:
A. DI SPIEZIO SARDO, M.D.
Department of Gynecology and Obstetrics
and Pathophysiology
of Human Reproduction
University of Naples "Federico II"
Naples (Italy)