

Case presentation

Intestinal type *in situ* adenocarcinoma of the cervix as a precursor of cervical signet ring cell adenocarcinoma

Adenocarcinom cervical in situ de tip intestinal, precursor al adenocarcinomului cervical cu celule "in inel cu pecete"

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Abstract

In the cervix, signet ring cell adenocarcinoma of the cervix is usually of metastatic origin. Only in rare cases it can develop as a primary, with only 12 cases reported to date. Characteristically, tumor cells with eccentric nuclei and pale basophilic cytoplasm are present in nests or clusters. We present here the case of a 41 year old patient diagnosed three years before of a mixed high grade cervical intraepithelial neoplasia (CIN III) and intestinal adenocarcinoma in situ that was excised by a cone biopsy. Cytologic follow-up for a period of 3 years revealed no abnormal cells. She eventually presented with a polypoid mass protruding through the external cervical os. The biopsy showed a solid proliferation of characteristic signet ring cells with immunohistochemical results that further supported a cervical immunophenotype. This is the first documented case demonstrating a precursor lesion of intestinal type adenocarcinoma for a primary infiltrating signet ring carcinoma of the cervix. Intestinal differentiation is almost invariably associated with invasive features.

Keywords: *intestinal in situ adenocarcinoma, signet ring cell adenocarcinoma, cervix*

Rezumat

Adenocarcinomul cervical cu celule în inel cu pecete este de obicei de origine metastatică. Foarte rar reprezintă o tumoră primară cervicală, până în prezent fiind raportate în literatura de specialitate doar 12 astfel de cazuri. Din punct de vedere microscopic tumora este constituită din celule tumorale ce prezintă nucleu localizat excentric și citoplasmă palidă bazofilă, celulele fiind dispuse architectural în cuiburi sau placarde. Prezentăm cazul unei paciente de 41 ani, diagnosticată cu neoplazie intraepitelială cervicală cu grad înalt de malignitate (NIC III) și adenocarcinom in situ de tip intestinal și tratată prin conizație. Urmărirea periodică pe parcursul a 3 ani după conizație prin examen citologic nu a identificat celule atipice. Examenul clinic efectuat

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dupa 3 ani evidentiaza o masă tumorală polipoidă localizata la cervical. Biopsia acestei formatiuni tumorale evidențiază o proliferare tumorală solidă formată exclusiv din celule tumorale în inel cu pecete. Examinările imunohistochimice confirmă originea cervicală a tumorii. Acest caz este primul care demonstrează faptul că adenocarcinomul cervical in situ de tip intestinal reprezintă o leziune precursoră pentru un adenocarcinoma infiltrativ primar cu celule în inel cu pecete. La nivel cervical diferențierea intestinală este frecvent asociată cu o componentă infiltrativă.

Cuvinte cheie: adenocarcinom in situ tip intestinal, adenocarcinom cu celule in inel cu pecete, cervix

Introduction

Signet ring adenocarcinoma of the cervix is a rare lesion with only 12 cases documented in the literature to date (1). Usually, the primary lesion is found in the breast, ovary or gastro-intestinal tract. Immunohistochemical analysis helps to confirm a primary cervical origin. This is the first publication documenting the fact that in situ intestinal type of cervical adenocarcinoma can be the precursor of this lesion since in this case the patient was previously diagnosed with a mixed high grade squamous cervical intraepithelial neoplasia (CIN III) and intestinal in situ adenocarcinoma on cone biopsy. This case also demonstrates the positive response to radiotherapy in signet ring adenocarcinoma, since no tumor cells were detected in the hysterectomy specimen after radiotherapy.

Case report

A 41 year old patient was diagnosed with HSIL (high grade squamous intraepithelial lesion) on a pap smear 4 years ago (2007), eventually, she underwent biopsy of the cervix followed by conization. CIN III associated with intestinal mucinous in situ adenocarcinoma were present on 4 of the 12 slides from the cone biopsy and in two of these slides, the in situ adenocarcinoma component being present adjacent to the surgical endocervical margin (*Figure 1*). For the next three years after the procedure, the patient had negative pap smears. In 2010, however, the patient presented with vaginal discharge and the gynecological examination revealed a friable polypoid cervical tumor protruding through the external cervical os. The

biopsy from the cervical tumor was solid in architecture and composed only of signet ring cells, containing abundant Alcian blue-positive intracytoplasmatic sialomucins, atypical nuclei and numerous mitotic figures (*Figures 2 and 3*). In order to rule out a metastasis from the breast, ovary or gastro-intestinal tract, mamography, ultrasound examination of the breast and pelvis and gastroscopy/colonoscopy were performed and were all negative. Also, immunohistochemical analysis showed that the tumor cells were positive for CK7, p16, CEA and negative for CK20, Vimentin, ER, PR (*Figures 4, 5, 6 and 7*). HPV detection showed the presence of the HPV 18 subtype. The patient underwent radiotherapy (9 cycles of 50GY/25FR/pelvis, 10 MV photon) followed by total hysterectomy together with bilateral salpingo-oophorectomy and locoregional lymph node dissection.

On macroscopic examination, a 35 mm diameter polypoid cervical tumour of soft consistency and grey colour was observed in the cervical canal (*Figure 8*). Microscopic examination of the tumour and cervical wall revealed only large pools of mucin deeply dissecting the cervical wall with no remaining tumor cells present after radiotherapy and no distant metastases in the other examined structures (*Figure 9*). She is well with no signs of local recurrence or distant metastases 2 years after the diagnosis.

Discussion

Signet ring cells can appear in the cervix in various conditions, from intestinal metaplasia and in situ intestinal type of adenocarcinoma to invasive signet ring cell adenocarcinoma of

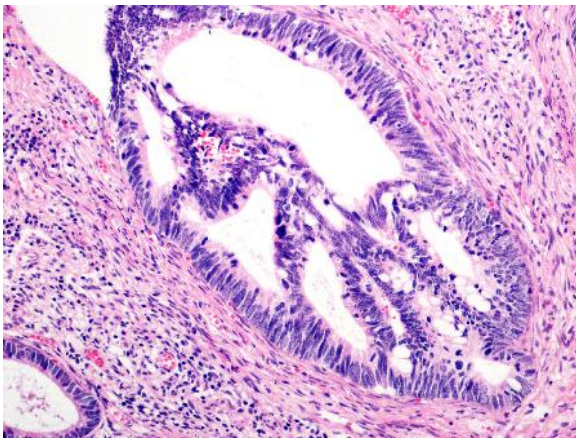


Figure 1. Area of intestinal mucinous in situ adenocarcinoma present on cone biopsy, x20, H-E

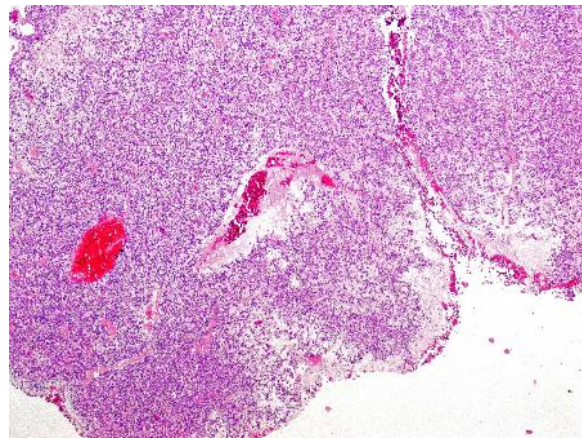


Figure 2. Solid proliferation of tumor cells of signet ring appearance, x4, H-E

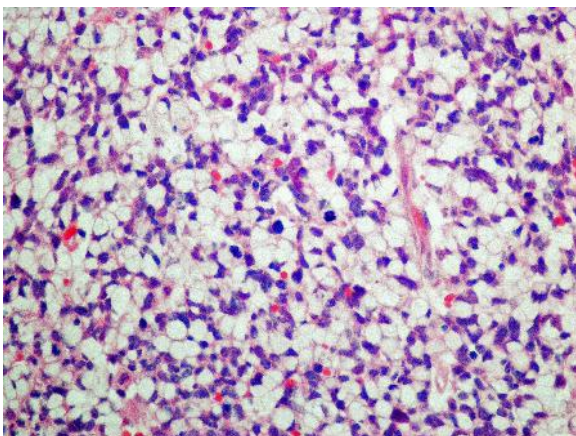


Figure 3. Higher magnification of signet ring cells, x20, H-E

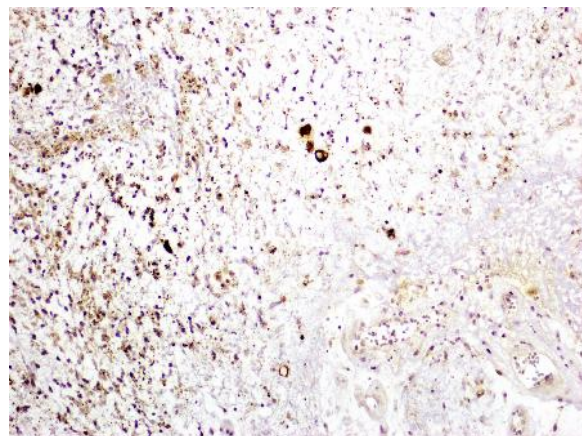


Figure 4. Tumor cells positive for anti-CK7 antibody, x10

primary or metastatic origin (2; 3). True intestinal metaplasia in the cervix in the absence of in situ adenocarcinoma is rare. Although it is known that sporadic goblet cells can appear in benign endocervical glands, features of intestinal metaplasia should raise a high index of suspicion for endocervical glandular dysplasia or even adenocarcinoma in situ intestinal type. The adenocarcinoma in situ of intestinal subtype is a lesion that develops in association with the Human papilloma virus (HPV) infection (4). There are no documented cases of intestinal in situ adeno-

carcinoma as a precursor of infiltrating mucinous adenocarcinoma in the cervix.

Signet ring cell tumors of the cervix, a variant of mucinous adenocarcinoma, are very rare primaries, with only 12 cases reported so far, most of the cases that have been reported being metastases from either breast, ovary or gastro-intestinal tract (1, 5). Among these primary ones, 8 had a major component of signet ring cells, 5 cases being associated with a classic endocervical mucinous type of infiltrating adenocarcinoma. Only 3 cases had a solid

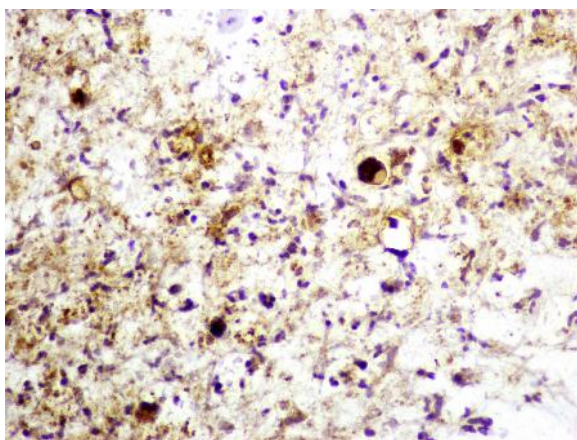


Figure 5. Tumor cells positive for anti-p16 antibody, x20

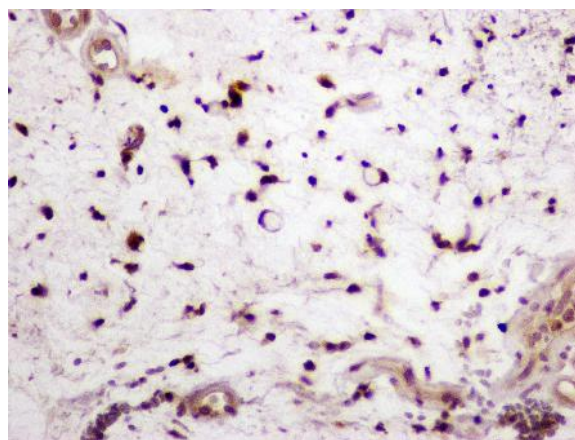


Figure 6 – tumor cells negative for anti-ER antibody, x20

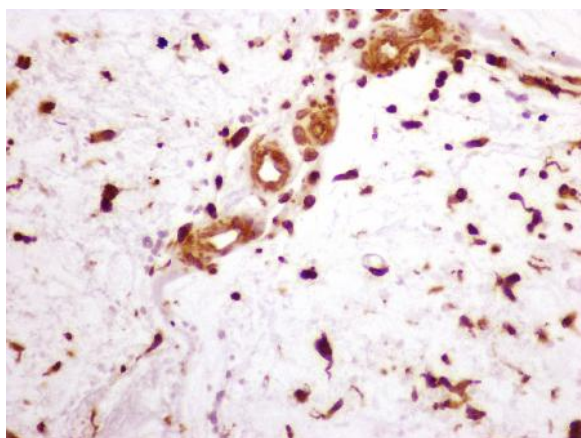


Figure 7. Tumor cells negative for anti-vimentin antibody, x20

architecture and one case was associated with an in situ adenocarcinoma (but not of intestinal type) while 1 case was associated with in situ adenocarcinoma and CIN III.

In our case, the biopsy had a solid architecture and was composed of only signet ring tumor cells with no areas of other infiltrating adenocarcinoma type. Furthermore, 4 years before diagnosis the patient underwent cone biopsy and a mixed lesion of CIN III and an intestinal type of in situ adenocarcinoma were diagnosed close to the surgical margins. This paper documents further,

that the presence of intestinal type of in situ adenocarcinoma in the cervix represents a risk factor for eventual invasion in premalignant glandular lesions and consequently, these patients should be treated with total hysterectomy, especially if the lesion is present in the surgical margins (6). The patient underwent radiotherapy and examination of the surgical specimen revealed no remaining tumor cells, with only pools of acellular mucin implying that this type of tumor has a good response to radiotherapy. This pattern is seen in cases of mucinous adenocarcinoma of the cervix after radiotherapy and it is known as „epithelium drop-out” with the residual cancer represented only by empty spaces filled with mucin. The „drop-out” pattern has been documented in mucinous adenocarcinoma of the cervix before but this is the first case of signet ring cell carcinoma with primary cervical origin associated with drop-out pattern in a post-treatment specimen.

The differential diagnosis in this case included areas of signet ring cells in a classic mucinous adenocarcinoma, squamous carcinoma with isolated signet ring cells, clear cell adenocarcinoma with signet ring cells, metastases of signet ring cell carcinoma from the breast, ovary, gastrointestinal tract and microglandular hyperplasia with signet ring cell morphology. The immunohistochemical analysis is useful in the diagnosis,



Figure 8. Polypoid cervical tumor with soft consistency and grey color, localized in the cervical canal

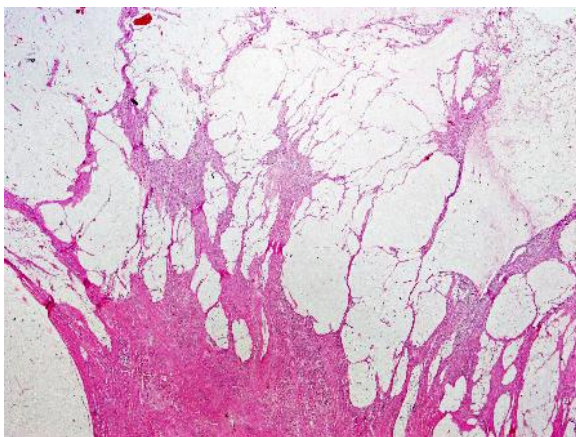


Figure 9. Pools of mucin dissecting the cervical wall with no remaining tumor cells after radiotherapy, x4, H-E

since these lesions have a different treatment depending on their origin. The primary signet ring cell adenocarcinoma is usually positive for CK7, CEA while CK20, ER, PR, GCDFP 15, CDX 2 are negative. However, the immunohistochemical results have to be used with caution since cases in

which a hybrid immunophenotype with CK 7 diffusely positive and CK 20 and CDX2 at least focally positive have been encountered, this partial enteric immunophenotype being similar to that observed in other intestinal lesions in the female genital tract like ovarian intestinal mucinous neoplasms. p16 was positive in three cases with HPV 18 detection in two cases. In our case, the markers confirmed the primary origin in the cervix and p16 positivity together with HPV detection of HPV18 established a correlation of the lesion with HPV infection.

Conclusions

This is the first documented case demonstrating intestinal type adenocarcinoma as a precursor lesion of a primary signet ring carcinoma of the cervix. Intestinal differentiation in the cervix and the presence of this type of lesion in the resection margins represent a risk factor for eventual invasion in premalignant glandular lesions. Conservative treatment is indicated in young patients if future fertility is desired only if the lesion is of small size and at distance from the surgical margins. This case also demonstrates the positive response to radiotherapy in signet ring cell adenocarcinoma radiotherapy.

Acknowledgement

The diagnostic contribution of Professor Francisco F. Nogales, University of Granada Spain is gratefully acknowledged in this case.

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