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Primary Signet Ring Cell Adenocarcinoma of the Uterine Cervix-A rare neoplasm that raises the question of metastasis to the cervix.

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Primary signet ring cell carcinoma is extremely rare, and must be distinguished from metastatic carcinoma to the cervix.

Keywords: cervix neoplasms, metastasis, signet ring cell carcinoma, adenocarcinoma, female, neoplasm staging.
Abstract:

Primary signet ring cell adenocarcinoma is extremely rare. Signet ring cell carcinoma is more commonly primary in the stomach or breast, and the more likely metastatic disease to the cervix needs to be ruled out. We present a case of primary signet ring cell carcinoma of the cervix and review the literature.
Introduction

Primary signet ring cell adenocarcinoma of the cervix is extremely rare, and most cases of signet ring carcinoma in the cervix are metastatic(1). Signet ring cell carcinoma is more commonly primary in the stomach, or breast, can also arise in the colon, and metastatic disease to the cervix from one of these or other less common sites needs to be ruled out. We present a case and review the literature.

Case

The patient was a 64-year-old female with a past medical history significant for bilateral retinoblastomas as a child and recent maxillary sinus leiomyosarcoma who now presented with abdominal fullness. A CT of the abdomen/pelvis revealed a large amorphous mass in the pelvis causing bilateral hydronephrosis resulting in placement of a unilateral nephrostomy tube. She subsequently underwent endometrial and endocervical curettage. The endometrial curettage showed poorly differentiated adenocarcinoma with signet ring features and no endometrial tissue. The endocervical curettage also showed poorly differentiated adenocarcinoma with signet ring cells infiltrating endocervical tissue. A PET/CT (Positron Emission Tomography - Computed Tomography) scan noted a large pelvic mass with increased activity in the lower uterine segment/cervix region with no other areas of FDG(fludeoxyglucose) uptake. She had many medical co-morbidities and her performance status was poor. As part of her tumor staging, an examination under anesthesia, LEEP(loop electroexcisional procedure) cone biopsy, vaginal biopsy and cystoscopy were performed. Examination under anesthesia revealed no palpable supraclavicular, axillary, or inguinal adenopathy. Her breast examination was negative for any
palpable breast nodularity. Her abdomen was scaphoid, and a 16-week size fibroid uterus could be palpated through the lower abdomen. On speculum, bimanual and rectovaginal examination, there was a 2 cm firm cervix with obliteration of the anterior fornix. There was palpable extension submucosally in the vagina at 1 o'clock. On rectovaginal examination, she had a bulky 16 to 18-week fibroid uterus without palpable parametrial disease on the left, however, on the right there was palpable disease through the parametria which was infiltrative and non-nodular. The rectum was smooth and there was no palpable rectal extension. The cystoscopy showed no lesions. The LEEP cone biopsy and vaginal biopsy showed adenocarcinoma characterized by small infiltrating cells with small signet ring-like intracytoplasmic lumina staining for periodic acid Schiff(PAS), growing in cords and sheets without desmoplasia, mimicking lobular carcinoma of the breast(figure 1). The immunohistochemical stains for Cytokeratin 7, Carcinoembryonic antigen(CEA), and P16 were positive and stains for estrogen receptor(ER), progesterone receptor(PR), Gross cystic disease fluid protein(GCDFP) a marker seen in breast lesions, S-100 protein, synaptophysin, smooth muscle actin(SMA), caudal-type homeobox 2(CDX-2, a marker for colon carcinoma) and Cytokeratin 20 were negative denoting the presence of non-gynecological tumor. The histology was most suggestive of lobular breast carcinoma, although at the time, metastatic gastric or pancreatic primaries were also suggested in the differential. Based on this pathology report, further work-up with esophagogastroduodenoscopy (EGD), colonoscopy and breast MRI were performed. The biopsies taken of the stomach, duodenum, colon and rectum showed no signs of neoplasm. The breast MRI performed showed a benign 0.3 cm lesion in the central lower left quadrant of the breast. The patient was referred to medical oncology and radiation oncology for palliative treatment for stage IVB adenocarcinoma of the cervix that was currently asymptomatic, however within three months, she developed palpable supraclavicular adenopathy and a right lower
extremity deep venous thrombosis. She was admitted to an outside hospital and referred for hospice care and expired shortly thereafter.
Discussion:

Primary adenocarcinoma of the cervix is usually endocervical or endometrioid in histology, with intestinal, villoglandular, and minimal deviation subtypes less common. Extremely rare is signet ring cell adenocarcinoma, a tumor most often arising in stomach or breast. Balci et al(1) reviewed the literature in 2010, reporting what they believed was the 12th case in the literature, and there have been a few reports since then(2). They emphasized the need to rule out metastatic disease to the cervix, and noted that identification of human papillomavirus in the tumor supports a cervical primary. Our case was p16 positive, in addition to the negative metastatic workup, suggestive of high risk HPV etiology. In one case(2), the tumor spread to the endometrium and myometrium, but was positive for p16 immunohistochemistry and HPV18 by PCR, supporting the cervical origin. Signet ring cell carcinoma may be the only histology seen, but admixtures with other histologic types, such as glassy cell carcinoma(3) have been reported. The number of reported cases is too low to establish a prognosis for this lesion, but it has been suggested that advanced stage disease is particularly aggressive(2,3,4). Low stage disease seems to have a better overall prognosis, much as usual cervical carcinoma, with one case of stage 1B1 reported as having an 8 year disease free survival at the time of the report(5).

Presenting symptoms on reported cases are similar to more usual cervical cancers, including abnormal bleeding, including postcoital bleeding(2). Rarely abnormal glandular cells may be seen on pap smears(6), however signet ring cells on a pap smear may also reflect metastatic carcinoma to cervix(7), or even gastrointestinal carcinoma with ascites without cervical involvement(8).

The pattern of the tumor described here was most suggestive of a primary lobular breast carcinoma, but was determined to be of cervical primary. Metastatic lobular carcinoma of the breast to the cervix has occurred as much as 15 years after therapy(9). It is critical to rule out
metastatic disease before determining that a signet ring cell carcinoma is primary to the cervix.

Although there are few reported cases, and survival documented in early stage disease, reported late stage disease appears to be aggressive.
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diagnosis of gastrointestinal cancer without cervico-vaginal metastases. Eur J Gyneaec Oncol

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Figure Legend:

Figure 1- The tumor infiltrated by individual cells in a pattern mimicking lobular breast carcinoma, with scattered signet ring cells (inset) with a globule of mucin pushing the nucleus to the side, creating the signet-ring appearance.