

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

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4 **Bernadette Cracchiolo, MD, MPH*, Theresa Kuhn, MD*,Debra Heller, MD**,****
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7 From the Departments of Obstetrics, Gynecology, and Women's Health*, and Pathology &
8 Laboratory Medicine **, Rutgers-New Jersey Medical School, Newark, NJ
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11
12
13 Address Correspondence to:

14 Debra S. Heller, MD

15 Dept of Pathology-UH/E158

16 Rutgers-New Jersey Medical School

17 185 South Orange Ave

18 Newark, NJ, 07103

19 Tel 973-972-0751

20 Fax 973-972-5724

21 hellerds@njms.rutgers.edu

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27 **Precis:**

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

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33 **Keywords:** cervix neoplasms, metastasis, signet ring cell carcinoma, adenocarcinoma, female,
34 neoplasm staging.

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

41 **Introduction**

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

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49 **Case**

50 The patient was a 64-year-old female with a past medical history significant for bilateral
51 retinoblastomas as a child and recent maxillary sinus leiomyosarcoma who now presented with
52 abdominal fullness. A CT of the abdomen/pelvis revealed a large amorphous mass in the pelvis
53 causing bilateral hydronephrosis resulting in placement of a unilateral nephrostomy tube. She
54 subsequently underwent endometrial and endocervical curettage. The endometrial curettage
55 showed poorly differentiated adenocarcinoma with signet ring features and no endometrial
56 tissue. The endocervical curettage also showed poorly differentiated adenocarcinoma with signet
57 ring cells infiltrating endocervical tissue. A PET/CT (Positron Emission Tomography -
58 Computed Tomography) scan noted a large pelvic mass with increased activity in the lower
59 uterine segment/cervix region with no other areas of FDG(fludeoxyglucose) uptake. She had
60 many medical co-morbidities and her performance status was poor. As part of her tumor staging,
61 an examination under anesthesia, LEEP(loop electroexcisional procedure) cone biopsy, vaginal
62 biopsy and cystoscopy were performed. Examination under anesthesia revealed no palpable
63 supraclavicular, axillary, or inguinal adenopathy. Her breast examination was negative for any

64 palpable breast nodularity. Her abdomen was scaphoid, and a 16-week size fibroid uterus could
65 be palpated through the lower abdomen. On speculum, bimanual and rectovaginal examination,
66 there was a 2 cm firm cervix with obliteration of the anterior fornix. There was palpable
67 extension submucosally in the vagina at 1 o'clock. On rectovaginal examination, she had a bulky
68 16 to 18-week fibroid uterus without palpable parametrial disease on the left, however, on the
69 right there was palpable disease through the parametria which was infiltrative and non-nodular.
70 The rectum was smooth and there was no palpable rectal extension. The cystoscopy showed no
71 lesions. The LEEP cone biopsy and vaginal biopsy showed adenocarcinoma characterized by
72 small infiltrating cells with small signet ring-like intracytoplasmic lumina staining for periodic
73 acid Schiff(PAS), growing in cords and sheets without desmoplasia, mimicking lobular
74 carcinoma of the breast(figure 1). The immunohistochemical stains for Cytokeratin 7,
75 Carcinoembryonic antigen(CEA), and P16 were positive and stains for estrogen receptor(ER),
76 progesterone receptor(PR), Gross cystic disease fluid protein(GCDFP)a marker seen in breast
77 lesions, S-100 protein, synaptophysin, smooth muscle actin(SMA),caudal-type homeobox
78 2(CDX-2, a marker for colon carcinoma) and Cytokeratin 20 were negative denoting the
79 presence of non-gynecological tumor. The histology was most suggestive of lobular breast
80 carcinoma, although at the time, metastatic gastric or pancreatic primaries were also suggested in
81 the differential. Based on this pathology report, further work-up with
82 esophagogastroduodenoscopy (EGD), colonoscopy and breast MRI were performed. The
83 biopsies taken of the stomach, duodenum, colon and rectum showed no signs of neoplasm. The
84 breast MRI performed showed a benign 0.3 cm lesion in the central lower left quadrant of the
85 breast. The patient was referred to medical oncology and radiation oncology for palliative
86 treatment for stage IVB adenocarcinoma of the cervix that was currently asymptomatic, however
87 within three months, she developed palpable supraclavicular adenopathy and a right lower

88 extremity deep venous thrombosis. She was admitted to an outside hospital and referred for
89 hospice care and expired shortly thereafter.

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93 Discussion:

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

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

114 The pattern of the tumor described here was most suggestive of a primary lobular breast
115 carcinoma, but was determined to be of cervical primary. Metastatic lobular carcinoma of the
116 breast to the cervix has occurred as much as 15 years after therapy(9). It is critical to rule out

117 metastatic disease before determining that a signet ring cell carcinoma is primary to the cervix.

118 Although there are few reported cases, and survival documented in early stage disease, reported

119 late stage disease appears to be aggressive.

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172 **Figure Legend:**

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

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