

Case report

Isolated metastatic pancreatic adenocarcinoma to the uterine cervix: A case report

Emily M. Hartsough^{a,*}, Britt K. Erickson^b, Anil Chauhan^c, Mahmoud A. Khalifa^a^a Department of Laboratory Medicine and Pathology, University of Minnesota, United States of America^b Department of Obstetrics, Gynecology and Women's Health, Division of Gynecologic Oncology, University of Minnesota, United States of America^c Department of Radiology, University of Minnesota, United States of America

ARTICLE INFO

Keywords:

Uterus

Cervix

Pancreatic adenocarcinoma

Metastasis

Gastric-type endocervical adenocarcinoma

ABSTRACT

The uterine cervix is an uncommon site of metastatic cancer. Specifically, pancreatic adenocarcinoma metastatic to the cervix is an exceptionally rarely reported phenomenon. We encountered a case of recurrent pancreatic adenocarcinoma presenting as a solitary metastasis to the cervix. To our knowledge, this is the only report describing an isolated recurrence of pancreatic adenocarcinoma to the cervix. When diagnosing metastatic disease to the cervix, it is also imperative for the clinician and pathologist to consider histologic mimics, such as the newly described gastric-type mucinous endocervical adenocarcinoma. Metastatic disease to the cervix may benefit from surgical resection.

1. Introduction

Metastatic disease to the cervix is an exceedingly rare phenomenon, with a reported incidence as low as 0.3% (Abrams et al., 1950; Mazur et al., 1984). Multiple factors likely contribute to the limited nature of this occurrence, including the small size, fibrotic stroma, and limited blood supply of the uterine cervix, particularly in post-menopausal women (Lemoine and Hall, 1986). Excluding direct extension of uterine, vaginal, or bladder malignancies, most of the metastatic disease to the cervix originates from other gynecologic sites (Lemoine and Hall, 1986; Mazur et al., 1984; Mulvany et al., 1996). Additionally, there are multiple case reports describing extra-pelvic metastases to the cervix, most often gastrointestinal, colorectal, and breast in origin (McCluggage et al., 2010; Pérez-Montiel et al., 2012). However, reports of metastatic pancreatic adenocarcinoma to the cervix are extremely limited. To our knowledge, there have only been three reports of pancreatic adenocarcinoma metastatic to the cervix, with no prior reports describing metastasis solely to the cervix (Boysen et al., 1951; Kinoshita et al., 2016; McCluggage et al., 2010). Here, we describe one patient with recurrence of pancreatic adenocarcinoma presenting as a solitary metastasis to the cervix.

2. Case Report

A 65-year-old woman with a history of stage III locally advanced

pancreatic adenocarcinoma was found to have an elevated Cancer Antigen 19-9 (CA 19-9) level and a cervical mass on follow-up tumor surveillance two years following her initial diagnosis. Her medical history was remarkable for type II diabetes, pulmonary embolism, hypothyroidism, asthma and bronchiectasis, obstructive sleep apnea, neuropathy, and vitreous hemorrhage. There was no known family history of pancreatic cancer. The patient had received regular cervical cancer screening and most recently had a normal Pap smear and negative HPV testing.

The patient initially was diagnosed with pancreatic adenocarcinoma during workup of a chronic cough. Imaging demonstrated a 2.3 cm mass in the pancreatic head, with subsequent fine needle aspiration biopsy revealing adenocarcinoma. Her CA 19-9 level at the time of diagnosis was elevated at 129 U/mL. She underwent three rounds of neoadjuvant chemotherapy with gemcitabine and albumin-bound paclitaxel, followed by exploratory laparotomy and Whipple procedure, including portal vein resection. Pathology was significant for a moderately differentiated adenocarcinoma of the pancreatic head (Fig. 1). The tumor microscopically invaded the duodenal wall, with associated perineural invasion. All margins were negative and lymph node dissection was negative (0/30). Pathologic staging at this time was ypT3N0. She subsequently received adjuvant chemotherapy with gemcitabine and capecitabine, with normalization of her CA 19-9 levels.

The patient was followed with CA 19-9 levels and surveillance

* Corresponding author at: Department of Laboratory Medicine and Pathology, University of Minnesota, 420 Delaware St. S.E. MMC 76, Minneapolis, MN 55455, United States of America.

E-mail address: hart1003@umn.edu (E.M. Hartsough).

<https://doi.org/10.1016/j.gore.2019.07.003>

Received 22 May 2019; Received in revised form 1 July 2019; Accepted 2 July 2019

Available online 04 July 2019

2352-5789/© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

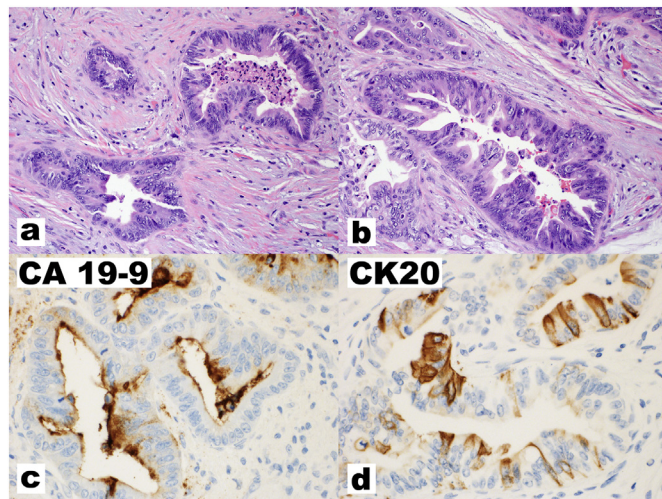


Fig. 1. Original pancreatic adenocarcinoma in the Whipple specimen. (A) Residual adenocarcinoma with no evidence of neoadjuvant chemotherapy response. Note the small malignant glands with pointed and angulated architecture. (B) Higher magnification showing the eosinophilic voluminous cytoplasm and the moderate to high nuclear atypia. (C) CA 19-9 immunopositivity along the luminal border of malignant cells. (D) Patchy immunopositivity with CK20.

imaging. Approximately two years following the patient's initial diagnosis, her CA 19-9 levels were found to be elevated to 228 U/mL. Contrast-enhanced CT images showed a heterogeneous, hypo-enhancing mass involving the cervix with extension into the lower uterine segment, measuring 2.7 cm, concerning for a malignant etiology (Fig. 2A & B).

The patient was referred to gynecologic oncology. Review of systems was notable for light vaginal bleeding for approximately two weeks as well as pelvic “tightness.” A physical exam and cervical biopsy were performed. The cervix was grossly normal appearing. On bimanual exam, the cervix was mobile, but globally enlarged and firm. Biopsy showed benign cervical stroma. Despite negative biopsies, there remained a high clinical suspicion for disease. Therefore, the patient was taken to the operating room for a cervical conization and Tru-Cut biopsies. Pathology demonstrated adenocarcinoma of the cervical stroma, likely of pancreatic origin. Immunohistochemical stains performed at this time were significant for positive CA 19-9, positive CK7, focal patchy positive CK20, and very focal positive CDX-2 (Fig. 3). Deep margins of the conization specimen were positive. Given the histologic and immunohistochemical diagnosis of recurrence, a whole body 18F-Fluorodeoxyglucose PET-CT exam was performed and was significant for a hypermetabolic cervical mass as well as an indeterminate 1.3 cm right lower mesenteric lymph node (Fig. 2C).

The patient was counseled on management options including systemic therapy versus resection. Given the potential of worsening bleeding and pelvic discomfort, the patient underwent robotic assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy. The decision was made to proceed with simple hysterectomy due to the lack of parametrial involvement on exam and the morbidity associated

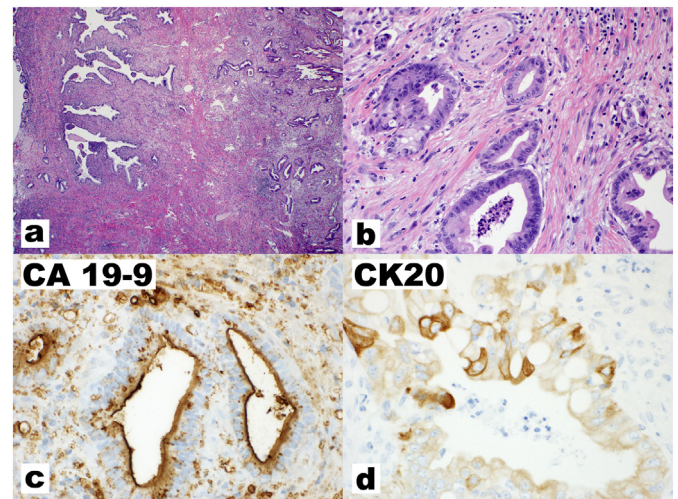


Fig. 3. Cervical cone biopsy with recurrent pancreatic adenocarcinoma. (A) Deep-seated infiltrative malignant glands disconnected from the normal-looking native mucosa. (B) Higher magnification showing small malignant glands with pointed ends and cells exhibiting eosinophilic voluminous cytoplasm and moderate nuclear atypia. (C) CA 19-9 immunopositivity along the luminal border of malignant cells. (D) Patchy immunopositivity with CK20.

with radical hysterectomy. Surgery was uncomplicated and she had a normal postoperative recovery. Final pathology revealed residual metastatic adenocarcinoma within the cervix forming an endocervical polyp, invading deeply into the outer half of the cervical wall, directly extending up the upper cervical canal and into the anterior and posterior lower uterine segment, and involving the overlying serosa posteriorly (Fig. S1). The background endometrium was atrophic and unremarkable with an endometrial polyp with focal atypical hyperplasia. The ovaries and fallopian tubes were negative for metastatic disease or malignancy, and the right ovary was notable for a mature cystic teratoma.

The patient declined further systemic therapy following hysterectomy. Six months following her hysterectomy, her tumor markers remain mildly elevated, but imaging shows no evidence of recurrent disease.

3. Discussion

Although metastatic disease to the cervix is a rare phenomenon, it needs to be considered when evaluating adenocarcinoma within the cervix. There are certain pathologic features that aid in distinguishing metastatic adenocarcinoma from endogenous endocervical adenocarcinoma. Extragenital metastatic disease to the cervix typically has characteristic patterns of involvement and distinguishing histologic features, such as predominant involvement of the deep cervical stroma, absence of precursor lesions, and lack of involvement of the cervical transformation zone (McCluggage et al., 2010; Mulvany et al., 1996).

Due to the low incidence of metastatic disease to the cervix, it can be difficult to determine what is primary versus metastatic disease. In fact, between 20 and 42% of metastatic cervical lesions may be



Fig. 2. CT images of cervical metastasis. Sagittal (A) and Axial (B) CT images demonstrate a heterogeneously enhancing large mass (arrows) centered on the cervix, which measured 2.7 cm. Fused Sagittal 18F-Fluorodeoxyglucose (FDG) PET-CT image (C) shows the cervical mass to be very FDG avid (circle), with standardized uptake value of 9.8. Additionally, there was an indeterminate 1.3 cm right lower mesenteric lymph node (not shown). Incidental note was made of intense physiologic uptake within the rectum, seen posterior to the cervical mass.

mistaken as primary cervical lesions, particularly in cases of adenocarcinomas of gastrointestinal origin (Mazur et al., 1984; Pérez-Montiel et al., 2012). While metastatic disease typically displays different morphology, there have been reported cases of metastatic disease of the cervix mimicking primary cervical adenocarcinoma or adenocarcinoma in situ, including a case of pancreatic adenocarcinoma (McCluggage et al., 2010). Kinoshita et al. (2016) also reported a case of pancreatic adenocarcinoma metastatic to the cervix that was initially misinterpreted as endocervical adenocarcinoma on endocervical brush cytology.

Primary endocervical adenocarcinomas present with a diverse set of histologic phenotypes, including endocervical (usual), endometrioid, intestinal, villoglandular, gastric, signet ring, clear cell, serous, and mesonephric. In particular, the newly described gastric-type endocervical adenocarcinoma is an important, and a rather potentially problematic, differential diagnosis. This is a rare aggressive variant of mucinous endocervical adenocarcinoma that is typically HPV negative. First, due to its rarity and its relative recent recognition, some pathologists may not be fully familiar with this entity. Secondly, there are considerable histologic similarities and overlap between gastric-type endocervical adenocarcinoma and metastatic pancreatic adenocarcinoma. Histologically, gastric-type endocervical adenocarcinoma consists of deeply invasive glands with marked variation in size and shape, composed of voluminous cells with eosinophilic or clear cytoplasm with distinct cell borders (Fig. S2), characteristically expressing HIK-1083 and MUC-6 (Kojima et al., 2007).

The immunohistochemical profile of primary endocervical adenocarcinomas is typically defined by positivity for p16 (strong and diffuse) and CEA antibodies, and negative immunostaining for ER and PR (Park et al., 2011). Immunohistochemistry may also be useful in the work-up of a cervical adenocarcinoma of unknown primary, such as CK7 and CK20. Additionally, if applicable, the patient's prior cancer history may be used to guide selection of immunohistochemical stains, such as CA 19-9 to confirm the diagnosis of metastatic pancreatic adenocarcinoma in our case. In addition, p16 positivity is often a helpful marker in identifying a usual-type primary cervical carcinoma, with HPV driving the majority of cervical squamous carcinomas and endocervical adenocarcinomas. Importantly, gastric-type endocervical adenocarcinoma is often negative for p16, as it is not related to HPV infection (Park et al., 2011).

Lastly, the clinical picture, including medical history, imaging results, and blood-based biomarkers are important resources to consider when forming a differential diagnosis for cervical adenocarcinomas. In fact, up to 80% of extragenital metastatic tumors to the cervix have a known primary (Mazur et al., 1984). In our case, the patient's elevated CA 19-9 and cervical mass two years following her initial diagnosis of pancreatic adenocarcinoma directed the clinical team to consider metastatic disease and take prompt surgical management. Additionally, metastatic disease is often accompanied by multi-organ involvement, as seen in the prior reports of pancreatic adenocarcinoma metastatic to the cervix (Boysen et al., 1951; Kinoshita et al., 2016; McCluggage et al., 2010). However, the cervix was the sole metastatic lesion identified in the patient from our institution.

4. Conclusion

In summary, metastatic disease to the cervix is a rare, yet possibly underrecognized phenomenon. This case presented uniquely as an isolated recurrence of pancreatic adenocarcinoma to the cervix, and pathologic similarity to gastric-type mucinous endocervical adenocarcinoma was an important differential diagnosis. Metastatic disease to the cervix is an important entity for clinicians and pathologists to consider, particularly in patients with previous cancer diagnoses.

Surgical management may be of benefit in the absence of widely metastatic disease.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2019.07.003>.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Disclosure

Research reported in this publication was supported to BKE by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number K12HD055887. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest statement

The authors of this paper have no relevant conflicts of interest relevant to the manuscript presented.

Author contributions

1. Emily Hartsough participated in manuscript writing and literature search.
2. Britt Erickson participated in manuscript development, medical record review, and patient care.
3. Anil Chauhan participated in manuscript writing and data acquisition.
4. Mahmoud Khalifa participated in developing study concept, manuscript writing, and data acquisition.

References

- Abrams, H.L., Spiro, R., Goldstein, N., 1950. Metastases in carcinoma. Analysis of 1000 autopsied cases. *Cancer* 3, 74–85. [https://doi.org/10.1002/1097-0142\(1950\)3:1<74::AID-CNCR2820030111>3.0.CO;2-7](https://doi.org/10.1002/1097-0142(1950)3:1<74::AID-CNCR2820030111>3.0.CO;2-7).
- Boysen, T.H., McCloskey, J.F., Sheffey, L.C., 1951. Carcinoma of the pancreas with metastasis to the cervix uteri. *Am. J. Obstet. Gynecol.* 61, 923–926. [https://doi.org/10.1016/0002-9378\(51\)90357-2](https://doi.org/10.1016/0002-9378(51)90357-2).
- Kinoshita, Y., Yoshizawa, K., Yuri, T., Tsubur, A., Shikata, N., 2016. Endocervical metastasis of pancreatic cancer: a rare case report of long-term survival. *Hum. Pathol. Case Rep.* 5, 34–38. <https://doi.org/10.1016/j.ehpc.2015.12.002>.
- Kojima, A., Mikami, Y., Sudo, T., Yamaguchi, S., Kusanagi, Y., Ito, M., Nishimura, R., 2007. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am. J. Surg. Pathol.* 31, 664–672. <https://doi.org/10.1097/01.pas.0000213434.91868.b0>.
- Lemoine, N.R., Hall, P.A., 1986. Epithelial tumors metastatic to the uterine cervix. A study of 33 cases and review of the literature. *Cancer* 57, 2002–2005.
- Mazur, M.T., Hsueh, S., Gersell, D.J., 1984. Metastases to the female genital tract. *Cancer* 53, 1978–1984.
- McCluggage, W.G., Hurrell, D.P., Kennedy, K., 2010. Metastatic carcinomas in the cervix mimicking primary cervical adenocarcinoma and adenocarcinoma in situ: report of a series of cases. *Am. J. Surg. Pathol.* 34, 735–741. <https://doi.org/10.1097/PAS.0b013e3181d6b8fd>.
- Mulvany, N.J., Nirenberg, A., Öster, A.G., 1996. Non-primary cervical adenocarcinomas. *Pathology.* 28 (4), 293–297. <https://doi.org/10.1080/00313029600169214>.
- Park, K.J., Kiyokawa, T., Soslow, R.A., Lamb, C.A., Olivia, E., Zivanovic, O., Juretzka, M.M., Pirog, E.C., 2011. Unusual endocervical adenocarcinomas: an immunohistochemical analysis with molecular detection of human papillomavirus. *Am. J. Surg. Pathol.* 35, 633–646. <https://doi.org/10.1097/PAS.0b013e31821534b9>.
- Pérez-Montiel, D., Serrano-Olvera, A., Salazar, L.C., Cetina-Pérez, L., Candelaria, M., Coronel, J., Montalvo, L.A.H., De León, D.C., 2012. Adenocarcinoma metastatic to the uterine cervix: a case series. *J. Obstet. Gynaecol. Res.* 38, 541–549. <https://doi.org/10.1111/j.1447-0756.2011.01747.x>.