Vaginal oligometastatic disease of colorectal primary: Report of a novel therapeutic approach

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Abstract
Vaginal oligometastatic disease of colorectal primary is a rare malignancy with few reported cases in the literature and no standardized treatment paradigm. We report on the definitive management of an unusual case of an elderly woman with the aforementioned disease. A 78-year-old African-American woman presented with vaginal spotting and was found to have a vaginal lesion. Final pathology was consistent with moderately differentiated adenocarcinoma of colorectal primary. Extensive work up, which included endoscopies, pathologic analyses, and imaging workup, did not reveal a primary gastrointestinal malignancy. The patient underwent partial vaginectomy and final pathology once again confirmed moderately differentiated adenocarcinoma of colorectal primary (CDX 2 and CEA positive, ER/PR, and CK 7 negative) with negative margins. She went on to receive adjuvant concurrent chemoradiation with 5-FU based chemotherapy. She received 45 Gy in 25 fractions to the whole pelvis followed by an HDR brachytherapy boost to 12 Gy in two fractions. Unfortunately, 10 months after completing radiation, she was found to have adenocarcinoma arising from a hepatic flexure colon polyp on colonoscopy. She required definitive surgical resection and was staged as mpT3N0M1. She received 12 cycles of 5-FU and at 2-year follow-up was found to be disease free with no evidence of locoregional recurrence or distant metastatic disease. Continued long-term follow up is warranted.

Keywords
Vaginal cancer, colorectal metastasis, oligometastatic disease, brachytherapy

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Background/introduction
Primary vaginal cancer, though rare, has two major histological types: squamous cell carcinoma (80%) and adenocarcinoma (15%).¹ Vaginal oligometastatic disease of colorectal primary is a rare malignancy with few reported cases in the literature and no standardized treatment paradigm. It must be distinguished via pathologic analysis from other vaginal malignancies and thorough work up of the patient is necessary to exclude other sites of disease and determine the optimal treatment paradigm. We report on the definitive management of an unusual case of an elderly woman with the aforementioned disease.

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A 78-year-old woman presented with 8 months of lower abdominal discomfort and occasional vaginal spotting. She had a hysterectomy many years ago for dysfunctional uterine bleeding with no malignancy noted at that time. On exam, she had a mass palpated on the rectovaginal septum. Exam under anesthesia revealed a posterior distal vaginal mass crossing the midline in both directions. No rectal involvement was noted. She underwent a vaginal biopsy, which revealed adenocarcinoma, which was highly suggestive of a colon primary. She had a PET/CT showing uptake within the vagina, anterior to the rectum, measuring up to 12.5 SUV (Figure 1). This corresponded to the distal vaginal mass palpated on exam. PET/CT was also negative for a GI primary or other metastatic disease. She had a colonoscopy showing multiple benign polyps in the colon (no rectal masses or polyps). A repeat colonoscopy showed multiple sessile serrated adenomatous, some with high grade dysplasia and MSI but none were invasive. Repeat vaginal biopsy still showed a non-gynecologic, likely gastrointestinal primary. Multidisciplinary consensus was for resection of the vaginal lesion. The patient underwent partial vaginectomy. EUA showed a 1.5 cm distal vaginal lesion that extended to the left side of the vaginal vault. Pathology revealed invasive moderately differentiated adenocarcinoma. CDX 2 was positive while ER and PR were negative. Pathology further showed CEA positive and CK 7 negative. Following surgery, patient had CT enterography and EGD, which were negative. Repeat PET/CT showed increased activity in the loops of bowel without a CT correlate (felt to be due to patient taking metformin). There was an area of FDG avidity with concordant wall thickening seen at the level of the rectum/anus, which was felt to relate to decompressed state. Whether this vaginal lesion was due to hematogenous disease spread from prior unidentified primary (or under-sampling of colorectal adenoma) or drop metastasis was unable to be determined after extensive workup. Extensive surgery, including lymph node sampling and exploration of the peritoneum, was not pursued as a primary tumor was not found after extensive workup.

**Treatment**

Her case was again reviewed in multidisciplinary tumor board and she was recommended to be managed as having vaginal oligometastatic disease of colorectal primary. She was advised to proceed with radiation for locoregional treatment. As we were not able to locate a colorectal source and were unsure if this was either colon or rectal primary, we felt obliged to treat the pelvis as would standardly be performed in rectal cancer to avoid potential regional nodal failure in the pelvis. Concern for potential pelvic nodal failure after vaginal cuff brachytherapy alone could make pelvic reirradiation more difficult. Furthermore, as the patient already had vaginal metastatic disease, it was felt that our patient was at higher risk for locoregional failure.

In the setting of oligometastasis, a stage between locoregionally confined disease and polymetastases, definitive therapy allows for durable disease control and in some cases offers patients a second opportunity for cure.² To this end, as the patient had an otherwise good performance status and reasonably long-life expectancy otherwise, aggressive definitive therapy to maximize the chance of cure, was pursued in her case. She underwent radiation to the pelvic and inguinal lymph nodes with concurrent 5-FU followed by cylinder-based vaginal brachytherapy. Radiation to the inguinal lymphatics was pursued as she had distal vaginal disease and there was concern, after departmental peer review, for drainage to the inguinal lymphatics. This was reasoned in part because salvage inguinal lymphadenectomy would prove

**Figure 1.** PET/CT showing uptake within the vagina, anterior to the rectum, measuring up to 12.5 SUV.
more morbid than prophylactic irradiation as seen in GROINSS-VII/GOG270. The chemotherapy was continuous infusion 5-FU 225 mg/m² daily. However, it was discontinued after one cycle due to poor patient tolerance and then re-started with dose reduction (200 mg/m²). The external beam portion of radiation was 45 Gy in 25 fractions to the pelvis and whole residual vagina. The target included the postoperative tumor bed, pelvic (internal and external iliac, presacral) nodes, and inguinal lymph nodes and was delivered using IMRT. Dose volume histogram, including normal tissue constraints and target volume coverage are noted in Figure 2. During treatment, she experienced brisk erythema in the treatment field as well as patchy moist desquamation in the skin folds and creases. She also experienced radiation proctitis and loose stools that were managed with Imodium. The brachytherapy portion was high dose rate brachytherapy with Ir-192 source performed using a 3 cm diameter vaginal cylinder giving 12 Gy in two fractions to the surface of the vaginal mucosa. The EQD2 to the tumor was 83.9 Gy. The EQD2 (D2cc) to the critical structures of the bladder, rectum, and small bowel were 56.9, 58.7, and 55.8 Gy respectively.

Outcome and follow up

At 3-month follow up, she was noted to have alopecia of external genitalia and hyperpigmentation. Speculum exam showed erythema and patchy mucositis of vaginal mucosa. She had no evidence of disease. She denied dysuria, diarrhea, constipation, hematochezia, vaginal bleeding, spotting, or discharge, and abdominal pain. At 6-month follow up, she continued to have no evidence of disease or significant treatment-related side effects.

However, during a surveillance colonoscopy 10 months after completion of radiation, she was found to have a new adenocarcinoma arising from hepatic flexure polyps. She was recommended to have a total colectomy but ultimately proceeded with a diagnostic laparotomy which was negative for peritoneal spread followed by right hemicolectomy with removal of the terminal ileum, cecum, and proximal transverse colon. Pathology revealed moderately differentiated adenocarcinoma in the distal hepatic flexure of the colon infiltrating through the muscularis propria into the pericolonic adipose tissue, stage mpT3 N0 M1. Also noted was a moderately differentiated adenocarcinoma of the proximal hepatic flexure infiltrating through the muscularis propria, mpT2N0M1. Margins were negative. Perineural invasion was noted in the distal hepatic flexure tumor; lymphovascular invasion was not. Six lymph nodes were removed and none were positive for metastatic spread. The tumor specimen was positive for MSI-H (loss of MLH1, PMS2), BRAFV600E mutation. Based on BRAFv600E mutation, which portends a worse prognosis, as well as her age and pre-existing grade 1 peripheral neuropathy, medical oncology recommended

![Figure 2. Dose volume histogram showing target volume coverage and normal tissue constraints for patient’s pelvic radiation treatment.](image-url)
adjuvant 5-fluorouracil, which she started along with leucovorin. She has been tolerating it well.

At 2-year follow up from recurrence, she completed 12 cycles of 5-fluorouracil. The dose was modified for tolerance, but actual dosing was not available in the chart. At 2 years after recurrence, she was found to be without evidence of disease as her CEA was stable and she had no CT imaging findings concerning for recurrence or metastases. She is maintained on active surveillance.

Discussion/conclusions

Primary vaginal cancer is a rare tumor, representing about 2% of primary gynecologic malignancies. Even rarer are metastases of colorectal primary to the vagina. A few cases of intestinal-type neoplasms of the lower female genital tract have been described over the last 35 years in the cervix, vagina, and vulva. When a patient presents with a malignant lesion in the vagina, standard workup includes ruling out vulvar or cervical origin of the cancer. As in this case, the pathologic finding of adenocarcinoma can be even more puzzling as squamous cell carcinomas constitute the vast majority of vaginal and cervical cancers. Therefore, metastasis from another site should be at the top of the differential for patients who present with adenocarcinoma in the vagina. Isolated vaginal metastasis have previously been reported in the literature. However, in these case reports, the primary lesion often has been found. Patients typically present with vaginal bleeding or discharge and a mass.

The adenocarcinoma in our patient was immunoreactive for CEA and CDX2 but not CK 7. CDX2 is a highly sensitive and specific marker for adenocarcinoma of intestinal origin. Colorectal carcinomas consistently express CDX-2. CK-7 is often found in ovarian, breast, and lung adenocarcinomas, but not carcinomas of the colon. Giving this particular staining pattern, this patient’s malignancy was thought to be of colorectal origin.

Typically, cancer metastasizes to the vagina through one of three routes: the lymphatics, direct extension through the Pouch of Douglas, or pathways via the fallopian tubes. In this patient, given her prior hysterectomy with bilateral salpingo-oophorectomy, lack of primary disease noted on initial workup, and node-negative disease noted at time of colorectal surgery, it is most likely that the method of spread was hematogenous rather than through direct invasion, via the fallopian tubes, or through the lymphatic system.

While optimal management has yet to be developed, surgical resection is felt to be appropriate to provide local control. Additionally, the paradigm for treatment of oligometastatic disease from palliative to curative is undergoing a shift. Multi-modality therapy, including tri-modality approaches, have been explored in those with vaginal metastases from colorectal primaries with mixed results. Extrapolation of data from primary vaginal cancer suggest a benefit to a combined chemoradiation followed by brachytherapy boost approach.

Multidisciplinary discussion is important to develop treatment plans as a combination of surgery, chemotherapy, and radiation, in our case appears to provide durable disease control. This patient underwent surgical resection of the only known site of disease (the vaginal metastasis) followed by chemotherapy and pelvic radiation to decrease locoregional recurrence. Finally, she underwent a vaginal brachytherapy boost with total dose similar to that which would be given for cervical or primary vaginal cancers (EQD2 ≥ 80). This regimen proved to be safe and tolerable for the patient. She is currently free of disease with minimal treatment side effects. The eventual discovery of hepatic flexure polyps containing grade 2 adenocarcinoma confirm our initial diagnosis of colorectal primary with vaginal drop metastasis and support our treatment pathway.

To date, this is the first modern report of the use tri-modality therapy including a brachytherapy boost for vaginal oligometastatic disease from colorectal primary continued long-term follow up is warranted to determine efficacy and toxicity.

Author contributions

Data collection and manuscript writing- SA and PNB. Manuscript review, edits, and feedback- All authors.

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