



Isolated Metastases to Multiple Genital Organs: a Curious Case of Metachronous Spread of Carcinoma Colon

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Introduction

Gastrointestinal malignancy accounts for the most common cause of extragenital primary spreading to female genital tract with colorectal carcinoma leading among them [1]. Ovary and vagina are the most common sites for spread. Synchronous presentation occurs more frequently than metachronous lesions [2]. Isolated tumor deposit to one or more genital organs is rare. The present case discusses regarding the metachronous presentation of carcinoma colon to multiple genital organs.

Case Report

A 58-year-old well preserved post-menopausal lady (BSA of 1.72), with no family history of colonic or genital malignancies and no known comorbidities, was diagnosed with adenocarcinoma of the sigmoid colon 5 years back for which she underwent anterior resection. Post-operative histopathology revealed adenocarcinoma, moderately differentiated, pT3N0M0. Patient received 12 cycles of adjuvant chemotherapy (FOLFOX regimen). After 5 years, she presented with post-menopausal bleeding with no other symptoms. She underwent fractional curettage, and the biopsy was consistent with adenocarcinoma, moderately differentiated with IHC positive for CK20 and CDX2 and negative for CK7 and ER. Thus, a diagnosis of metastatic carcinoma colon to uterus was made and patient further evaluated.

PET-CT scan revealed metabolically active lesion in the fundus of the uterus with few metabolically active interaortocaval and left para-aortic nodes and no other sites

of metastasis (Fig. 1a, b). Colonoscopy was normal, and CEA was 10.5 ng/ml. After a multidisciplinary tumor board discussion, she was planned for surgery. Total abdominal hysterectomy with bilateral salpingo-oophorectomy with excision of right distal ureter and repair with DJ stenting, bilateral pelvic, and para-aortic and aortocaval nodal dissection was done. Intraoperatively, there was a nodule of 2.5 × 2.5 cm on the fundus of the uterus. Right ovary was replaced by hard mass adherent to the right ureter (Fig. 1a). Enlarged interaortocaval node of 2 cm was found.

Post-operative histopathology revealed uterine lesion extending from the endometrium to the myometrium, and 1 mm away from the serosal aspect of uterus showed metastatic adenocarcinoma deposit. Right ovarian mass with involved fallopian tube and adhered ureter showed metastatic adenocarcinoma deposit. Left ovary was normal. Cervical stroma was infiltrated by adenocarcinomatous deposits (Fig. 1b, c). Bilateral pelvic and interaortocaval nodes were free of tumor. Tumor cells showed positivity for CDX2 and CD20 and negative for vimentin, confirming origin from colon. Due to lack of funds Ras Mutation and MSI status analysis were not performed.

Post-operatively, she was given chemotherapy, 8 cycles of CAPOX. Patient is disease free at 32 months. CEA levels done at 6 monthly intervals were stable between 5–6 ng/ml

Discussion

Colorectal carcinoma is the third most common cancer diagnosed worldwide after breast and lung [3]. Spread to liver and lung are the most common sites of metastases from colorectal cancers followed by peritoneal surface deposits [3]. Metastases to genital organs occur usually as a part of widespread disseminated tumor. Isolated metastases to multiple female reproductive organs alone are uncommon.

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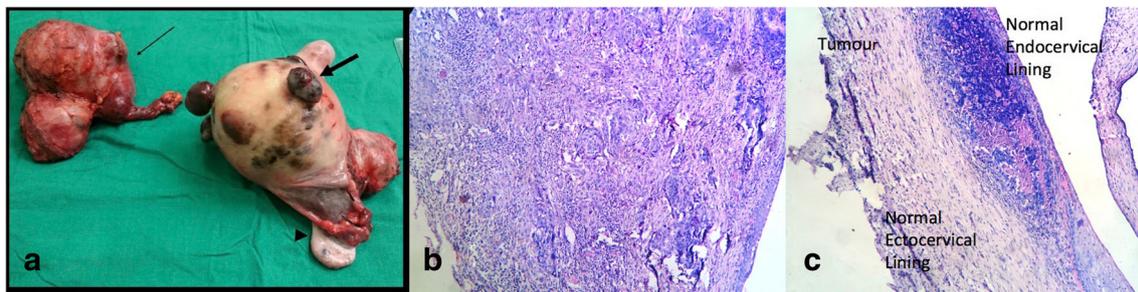


Fig. 1 a Specimen showing uterus with deposits (thick arrow), right ovarian mass with adherent ureter removed en bloc (thin arrow). Left ovary was within normal limits (arrowhead). b and c Normal ectocervical lining subepithelium shows infiltration by tumor

Colorectal cancer is the most common cancer metastasizing to the ovary worldwide [1]. Overall prevalence of ovarian metastases in colorectal cancer is 2.7% with isolated ovarian metastasis seen in half of them and about 1.1% cases present as metachronous lesions [4, 5]. The first suggested route of spread is by local invasion with direct extension of the primary tumor. The second proposed course of spread is via transcoelomic route where tumor cells could be implanted in the fallopian tube or uterus [6]. The other two suggested metastatic routes are lymphatic and hematogenous spreads. For lymphatic spread, there is a possibility of metastasis from the sigmoid colon lymphatics to the iliac and hypogastric lymph nodes where retrograde spread to the periurethral area, lower uterine, and anterior vaginal wall can occur [6]. Venous channels may allow metastatic cells to travel from the primary site in the colon to the ovarian plexus or parametrial veins and, hence, metastasis to ovaries and uterus [6]. Risk of ovarian metastasis is higher in premenopausal women due to high vascularity and raw surface after ovulation attracting surface deposits.

Metastasis to uterus from extragenital site is seen in less than 10% of cases of those affecting female genital tract with breast and colorectal cancers being the commonest. Uterine involvement usually involve ovary as the first site of metastasis and further involvement of the uterus has been proposed as secondary to lymphatic spread from ovaries. Within the uterus, metastasis involves myometrium in 96.2% cases and only endometrium in 3.8% cases. 32.7% of the cases had both myometrial and endometrial involvement [7].

Secondaries to the uterine cervix from extragenital sites are very rare comprising about 3.4% of cases of metastasis to female genital tract [7]. In a recent review by Matsuura, only 35 cases of secondary adenocarcinoma of the uterine cervix of extragenital primaries were reported in literature with colorectal carcinomas comprising 18.5% of them [8]. Reasons for infrequent involvement had been stated as high fibrous content, small size and limited blood flow, centrifugal lymphatic drainage, and infrequent diagnosis in patients already diagnosed with extragenital primary tumor.

Metastasis to more than one genital organ in the absence of widespread disseminated disease is uncommon. Mazur et al.

found metastasis in two genital organs in 13 patients [7]. Yasin et al. reported a case of rectal carcinoma metastasizing to the endometrium, ovaries, and fallopian tubes [9]. In our case, there were noncontiguous metastases to the ovary, endometrium, and cervix, which presented in metachronous settings representing hematogenous deposits.

The question still unanswered is whether the involvement of one of the genital organs warrants resection of other organs also. As the involvement of the uterus occurs secondary to lymphatic spread from the ovaries, theoretically, involvement of ovaries warrants resection of the uterus also [7].

Genomic or genetic studies can help us to evaluate the metastatic potential of the disease and can also alter treatment regimes. In the era of biological agents, addition of agents targeting the EGFR and VEGFR receptors to first-line chemotherapy regimens has shown to increase the progression-free survival and overall survival [10, 11]. Benefit from monoclonal antibodies targeting the EGFR is restricted to patients whose tumors do not contain mutated RAS genes or a BRAF V600E mutation [12, 13]. Accumulating evidence suggests that for patients with RAS/BRAF wild-type tumors, benefit from initial therapy with an anti-EGFR agent versus bevacizumab is also influenced by the sidedness of the primary tumor [14]. Immune checkpoint inhibitors are active for patients with dMMR, MSI-H tumors [15]. Even Her 2neu therapy has shown promise in this setting of metastatic disease [16]. Further studies are required to evaluate the role of surgery in the present era, where many treatment options are available in the armamentarium against metastatic colorectal cancer. Unfortunately, in our patient, biological treatments were not administered due to cost constraints. Complete resection of disease followed by adjuvant treatment resulted in almost a 3-year disease-free survival.

Circulating tumor cells (CTC), detected preoperatively, represent a valid prognostic factor for cancer progression and survival [17]. In the post-curative resection setting, their presence is associated with increased incidence of metastasis and decreased DFS [18]. In the metastatic setting, they can be both prognostic markers and predictive markers and help in assessing the response to systemic therapy [18].

Conclusion

This is the first case of carcinoma colon reported in literature metastasizing to the uterus, ovary, and cervix without any other site of metastasis. Any lady presenting with postmenopausal bleeding following treatment of any gastrointestinal malignancy, particularly colorectal malignancy, a differential of metastasis, should be considered and treated accordingly.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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References

- Mutter GL, Prat J (2014) Pathology of the female reproductive tract. Elsevier Health Sciences 2821 p
- Garrett CR, George B, Viswanathan C, Bhadkamkar NA, Wen S, Baladandayuthapani V, You YN, Kopetz ES, Overman MJ, Kee BK, Eng C (2012 Sep) Survival benefit associated with surgical oophorectomy in patients with colorectal cancer metastatic to the ovary. *Clin Colorectal Cancer* 11(3):191–194
- Riihimäki M, Hemminki A, Sundquist J, Hemminki K (2016) Patterns of metastasis in colon and rectal cancer. *Sci Rep* 6:29765
- Omranipour R, Abasahl A (2009) Ovarian metastases in colorectal cancer. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc* 19(9):1524–1528
- Segelman J, Flöter-Rådestad A, Hellborg H, Sjövall A, Martling A (2010) Epidemiology and prognosis of ovarian metastases in colorectal cancer. *Br J Surg* 97(11):1704–1709
- Marchal F, Leroux A, Hoffstetter S, Granger P (2006) Vaginal metastasis revealing colon adenocarcinoma. *Int J Colorectal Dis* 21(8):861–2. <https://doi.org/10.1007/s00384-004-0734-x>
- Kumar NB, Hart WR (1982 Nov) Metastases to the uterine corpus from extragenital cancers. A clinicopathologic study of 63 cases. *Cancer* 50(10):2163–2169
- Matsuura M, et al (2014) Metastatic carcinoma of the uterine cervix from rectal carcinoma: a case report and review of the literature. *Open Journal of Obstetrics and Gynecology* 4:617–620
- JK-PRACTITIONER JAN-MAR 2011 - jabt11i1p99.pdf
- Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. 2004 Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350(23):2335–42. <https://doi.org/10.1056/NEJMoa032691>
- Van Cutsem E, Köhne C-H, Láng I, Folprecht G, Nowacki MP, Cascinu S, et al. (2011) Cetuximab Plus Irinotecan, Fluorouracil, and leucovorin as first-Line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol* 29(15):2011–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21502544>. Accessed 23 Nov 2018
- Chung KY, Shia J, Kemeny NE, Shah M, Schwartz GK, Tse A, et al. (2005) Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol* 23(9):1803–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15677699>. Accessed 23 Nov 2018
- Rowland A, Dias MM, Wiese MD, Kichenadasse G, McKinnon RA, Karapetis CS, et al. 2015 Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. *Br J Cancer* 112(12):1888–94. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25989278>. Accessed 23 Nov 2018
- Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V 2017 The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur J Cancer* 70:87–98. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27907852>. Accessed 23 Nov 2018
- Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz H-J, Morse MA, et al. 2017 Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 18(9):1182–91. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28734759>. Accessed 23 Nov 2018
- Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, et al. 2016 Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 17(6):738–46. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27108243>. Accessed 23 Nov 2018
- Jia S, Zhang R, Li Z, Li J (2017) Clinical and biological significance of circulating tumor cells, circulating tumor DNA, and exosomes as biomarkers in colorectal cancer. *Oncotarget* 8(33):55632–45. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28903450>. Accessed 23 Nov 2018
- Steinert G, Schölch S, Koch M, Weitz J (2012) Biology and significance of circulating and disseminated tumour cells in colorectal cancer. *Langenbeck's Arch Surg* 397(4):535–42. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22350614>. Accessed 23 Nov 2018