Gynecologic Oncology Reports 26 (2018) 49–52

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Mullerian carcinosarcoma in the colon of a patient with history of endometrial carcinoma: A case report and insight into possible pathogenesis

Claire Anne Therese Hemedez[1], Michele Lomme*, M. Ruhul Quddus

Department of Pathology, Women and Infants Hospital, Providence, RI 02905, USA

ARTICLE INFO

Keywords:
Carcinosarcoma
Endometrioid carcinoma
Endometriosis
Epithelial-mesenchymal transition
Endometriosis associated intestinal tumor

1. Introduction

Carcinosarcoma is a rare gynecologic tumor of postmenopausal women encountered in 2–3% of uterine and roughly 1% of ovarian malignancies (Wells et al., 2014; Booth et al., 2004; Ferrandina et al., 2007). Even rarer is its presentation in the intestinal tract and delineation of tumor pathogenesis is complicated by its mullerian characteristics. When identified in colon, recurrence and/or metastasis from a gynecologic primary must be ruled out. Here we present a case of a mullerian carcinosarcoma in the rectosigmoid colon with a rather confounding history of endometrial carcinoma.

2. Case report

A postmenopausal 58 year-old obese Caucasian woman presented with recto-vaginal pain and severe constipation. Her past surgical history is significant for cholecystectomy in 1995 and robotic hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection for endometrial carcinoma four years ago. At the time of hysterectomy, the cecum was noted to be adherent to the anterior abdominal wall by dense fibrosis. Gross examination of the surgical specimen revealed a 462-gram uterus with smooth serosa. The endometrial cavity showed a 3.0 × 2.0 cm. slightly exophytic tumor without gross myometrial invasion. Extensive sampling per departmental protocol and subsequent microscopic examination revealed a FIGO grade 2 endometrioid adenocarcinoma (Fig. 1) confined to the endometrium. Lymphovascular space invasion was not identified. Bilateral ovaries revealed endometriotic cysts. Thirty pelvic and paraaortic lymph nodes were negative for metastatic carcinoma. Immunostaining for mismatch repair (MMR) proteins showed loss of MLH1 and PMS2. Subsequent methylation testing revealed MLH1 hypermethylation. The final AJCC staging of the tumor was T1aN0 (FIGO 1A). The patient was placed under surveillance with no additional treatment.

At current presentation, physical exam revealed a soft and non-tender abdomen with no palpable lesions. However, colonoscopy showed a 1.5–2.5 cm submucosal lesion protruding into the lumen of the rectosigmoid colon, with normal overlying mucosa. Initial colonic biopsies were negative for dysplasia or malignancy but a subsequent IR-guided biopsy, performed at an outside institution, showed adenocarcinoma favoring recurrence of the endometrial tumor. This was based on positive immunostaining for CK7 and Pax8, negative CDX2 and GATA3 stains, and aberrant loss of MLH1, PMS2 and MSH6. The patient underwent low anterior resection with colorectal anastomosis. Gross examination of the rectosigmoid resection revealed a 5.5 cm. colonic mass in the wall of the bowel involving the submucosa and extending to the pericolic fat. No mucosal involvement was noted. The cut surface of the tumor appeared white, fleshy to solid, with focal cystic areas. (Fig. 2a). The serosa was unremarkable. Microscopic examination revealed an endometrioid carcinoma, morphologically similar to that of her previous endometrial tumor, with focal clear cell and squamoid differentiation (Fig. 2b–d). Unexpectedly however, frank stromal sarcoma with focal chondromyxoid differentiation was also present. Biopsies from the pelvic sidewalls were negative for malignancy or endometriosis.

On immunostains, cytokeratin was diffusely positive in all epithelial components, and staining for vimentin demonstrated positivity in the

* Corresponding author.
E-mail address: mlomme@wihri.org (M. Lomme).
[1] St. Luke's Medical Center, Quezon City, Philippines, 1112.

https://doi.org/10.1016/j.gore.2018.09.003
Received 3 August 2018; Received in revised form 21 September 2018; Accepted 23 September 2018
Available online 24 September 2018

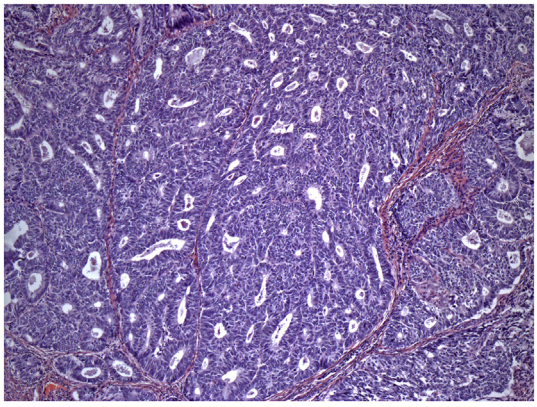

Fig. 1. Endometrial lesion on hysterectomy showing an endometrioid adenocarcinoma, Hematoxylin and Eosin stain, 10×.

stromal component (Fig. 3a–c). Endometrial stroma around the endometrioid component was also highlighted by CD10 positivity (Fig. 3d–e). Table 1 summarizes the results of the immunostains performed on the endometrial biopsy, hysterectomy and colonic tumor specimens. Ultimately, the colonic tumor was diagnosed as a pelvic carcinosarcoma. The patient is scheduled for chemotherapy after ileostomy reversal.

3. Discussion

First coined by Virchow in 1864, the term carcinosarcoma was used to describe a biphasic tumor with carcinomatous and sarcomatous elements (Ferrandina et al., 2007; Pang et al., 2018). The epithelial (most often endometrioid or serous types) and sarcomatous (most often high grade) elements of carcinosarcomas are intermixed (Wells et al., 2014). In the past, prevailing theories on its etiology included "collision" of two independent tumors then forming one tumor and the "combination" of masses which undergo divergence from a common prescursor stem cell. Recent studies suggest that these tumors are monoclonal in origin and that the epithelial component develops to the sarcomatous component through metaplasia (Cherniack, et al., 2017; Shaco-Levy and Piura, 2008). Of note similar tumors in breast are designated as "Metaplastic carcinoma". This biologic process of epithelial-mesenchymal transition (EMT) allows a polarized epithelial cell to undergo biochemical changes enabling it to display mesenchymal properties. In the context of tumor growth and cancer progression, genomic alterations enable cancer cells to invade and spread through EMT and revert back (mesenchymal-epithelial transition; MET) to the original epithelial phenotype which some studies suggest as a requisite for secondary tumor localization (Kalluri and Weinberg, 2009; Stewart and McCluggage, 2013).

Some intriguing questions may be put forward regarding the pathogenesis of the current case. Carcinoma recurring as a carcinosarcoma is exceedingly rare but has been reported. Applying the EMT-MET process, one could argue that the primary endometrial carcinoma recurred in the colon as a carcinosarcoma. Indeed, the endometrioid component of the colonic tumor has similar morphology to the prior endometrial tumor and both tumors showed MLH1 hypermethylation. Genomic alterations during transition could explain morphologic differences of the carcinomatous component (clear cell and squamoid differentiation) and the difference in staining pattern for PTEN in the two tumors supports that view. However, arguing against recurrence is the prolonged time to recurrence. Case reports describe 5 month to 2 year intervals prior to tumor recurrence. In those reports the primary endometrial tumors were both poorly differentiated and showed significant (> 50%) myometrial invasion (Ferrandina et al., 2007; Shaco-Levy and Piura, 2008). Prognosis was quite poor for those recurrences and patients succumbed to the disease within one year of diagnosis (Slavin et al., 2000). The FIGO 2 endometrioid carcinoma in this patient was non-invasive and without lymph-vascular space invasion.

Perhaps a more plausible explanation is that this represents a new tumor arising in association with endometriosis. Although no frank endometriosis was noted in the pelvis during laparoscopic hysterectomy four years ago, endometriosis was identified in both ovaries and a portion of the colon was adherent to the anterior abdominal wall in the absence of diverticulitis – a finding not uncommon in patients with pelvic endometriosis. The presence of CD10+ endometrial stromal cells in the colonic tumor, and the clear cell carcinoma component, a subtype of carcinoma well known to be associated with endometriosis, also supports this possibility.

Endometriosis is frequently multifocal, far more common than endosalpingiosis in the pelvis (ratio of 15:1) (Quddus et al., 2000). It occurs in the bowel in about 37% of patients (Agito et al., 2013) and can serve as a microenvironment for potential malignant transformation (Slavin et al., 2000). Malignant transformation of endometriosis (also known as endometriosis associated intestinal tumor) has been described in the literature, with 77% of cases occurring in the rectosigmoid colon. About a quarter of patients will give no history of endometriosis (Slavin et al., 2000). The risk is greatest among women who have been given hormone (estrogen) therapy. Increased fat stores can also induce hyperestrogenic states (Agito et al., 2013). The etiology of the lesion has been described as likely to be development of endometriosis from a mullerian rest or peritoneal mesothelium which subsequently develops into a malignant entity (Booth et al., 2004). Epigenetic inactivation of MLH1 has been implicated in the malignant transformation of ovarian endometriosis. A study showed that the frequency of promoter hypermethylation of MLH1 in cases of endometriosis associated ovarian carcinoma is higher than those of endometriosis alone (Ren et al., 2012).

Additional questions can be raised in this case include whether the sarcomatous component was overlooked in the prior tumor. The original endometrioid carcinoma was re-examined. The tumor was well sampled and there was no evidence of sarcoma. Also, in any tumor arising in the colon, a primary colonic carcinoma must be ruled out. In 1925, Sampson set criteria for malignancies arising in endometriosis of the colon, which include presence of benign endometriosis, endometriosis present in close proximity to malignancy and malignant tissue histology with endometriotic origin and no suggestion of metastasis (Booth et al., 2004; Agito et al., 2013). The bulk of these tumors are frequently located in the outer bowel wall and microscopically will not show adenomatous glandular mucosal changes or dirty luminal necrosis (Slavin et al., 2000; Agito et al., 2013). These features are consistent with the case we are reporting.

4. Conclusion

We report a rare case of carcinosarcoma in the wall of the rectosigmoid colon in a patient with a prior history of endometrial endometrioid carcinoma. Rare cases of carcinosarcoma have been reported in intesitinal endometriosis. Even rarer is the report of carcinosarcoma in a patient with prior history of endometrial carcinoma. Any such lesion in the colon should be properly examined and adequately sampled in order to confirm the diagnosis. It appears prudent to follow-up patients with endometrial carcinoma more closely should they have endometriosis. These patients already have underlying molecular alterations for carcinoma, and endometriosis elsewhere, if not managed, may offer a fertile ground for additional mullerian tumors. Much needs to be known regarding how endometriosis transforms into a malignant lesion and what role MLH1 hypermethylation might play in this process.

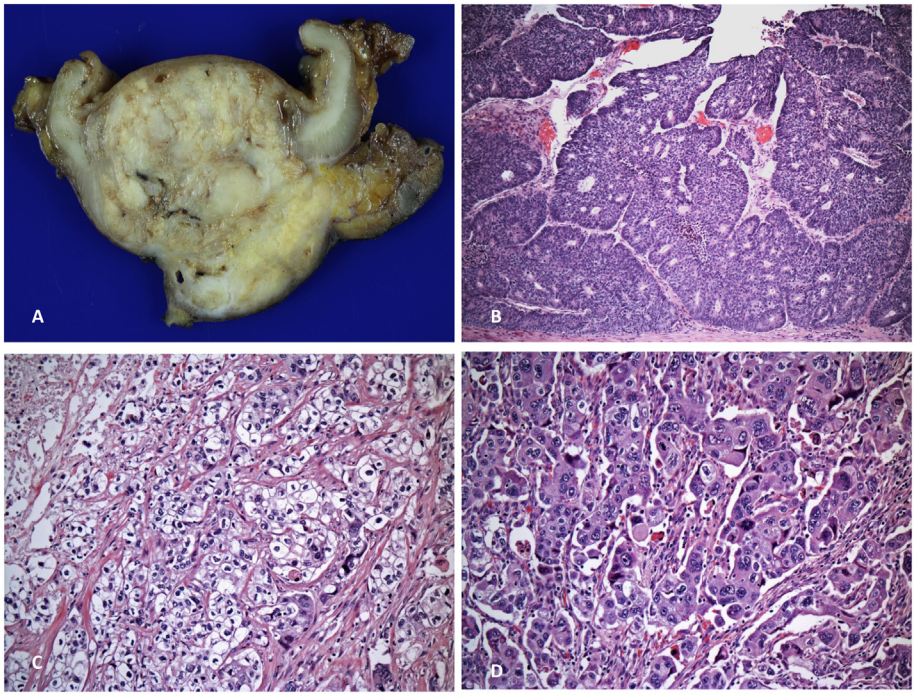

Fig. 2. A section of the solitary lesion (a) in the rectosigmoid colon showing no mucosal involvement. The tumor involved the submucosa up to the pericolic fat. Microscopic sections showed (b) endometrioid (magnification 10×), (c) clear cell and (d) squamoid components, Hematoxylin and eosin stain, 20×.

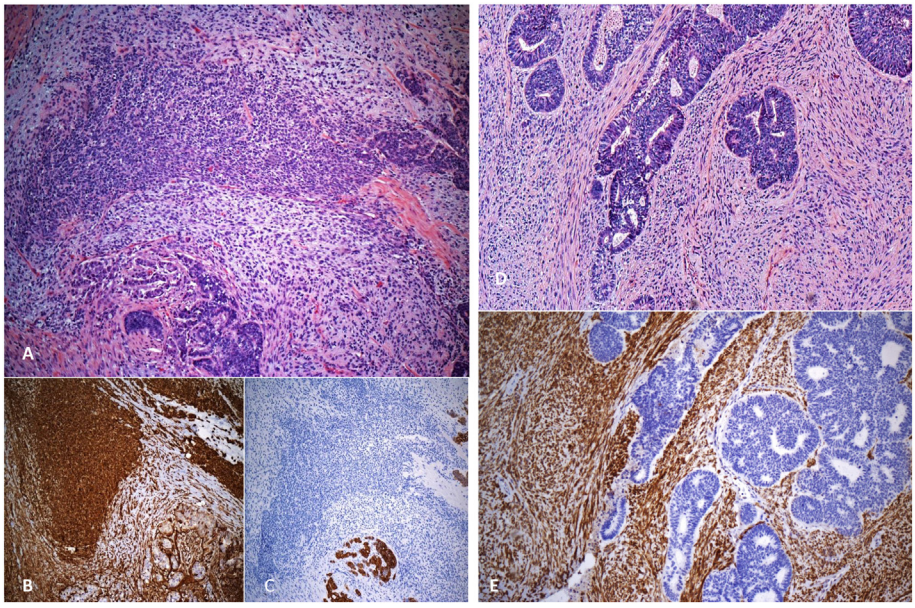

Fig. 3. (a) An area showing a solid sheet of cells embedded in a chondromyxoid matrix, hematoxylin and eosin stain, 10×. These cells are highlighted by immunostaining with (b) vimentin and negative staining for (c) cytokeratin, 10×. (d) The endometrioid component with stroma, Hematoxylin and eosin stain, 10×. The stroma is highlighted by (e) CD10 immunostaining, 10×.

Table 1
Results of immunohistochemical stains on the endometrial biopsy, hysterectomy and colon tumor.

	Endometrial biopsy	Tumor from hysterectomy	Colonic tumor
PTEN	Intact	–	Loss in epithelial component Intact in mesenchymal component
Beta-catenin	Positive, membranous staining	–	Positive membranous staining
MMR proteins	–		
MLH1		Loss of nuclear expression	Loss of nuclear expression
MSH2		Intact nuclear expression	Intact nuclear expression
MSH6		Intact nuclear expression	Intact nuclear expression
PMS2		Loss of nuclear expression	Loss of nuclear expression
MLH1 hypermethylation	–	Positive	Positive

Author contribution

Each named author has substantially contributed to the intellectual content of this manuscript and each has reviewed the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest

References

Agito, M.D., Rehmus, E.H., Powell, A.T., 2013. Mullerian carcinosarcoma arising from intestinal endometriosis. J. Clin. Oncol. 31 (11), e175–e177.

Booth, C., Zahn, C.M., McBroom, J., Maxwell, G.L., 2004. Retroperitoneal mullerian carcinosarcoma associated with endometriosis: a case report. Gynecol. Oncol. 93, 546–549.

Cherniack, A.D., Shen, H., Walter, V., Steward, C., Murray, B.A., Bowlby, R., Hu, X., Ling, S., Soslow, R.A., Broaddus, R.R., Zuna, R.E., Robertson, G., Laird, P.W., Kucherlapati, R., Mills, G.B., The Cancer Genome Atlas Research Network, Weinstein, J.N., Zhang, J., Akbani, R., Levine, D.A., 2017. Integrated molecular characterization of uterine carcinosarcoma. Cancer Cell 31, 411–423.

Ferrandina, G., Zannoni, G.F., Martinelli, E., Vellone, V., Prisco, M.G., Scambia, G., 2007. Endometrial carcinoma recurring as carcinosarcoma: report of two cases. Pathol. Res. Pract. 203, 677–681.

Kalluri, R., Weinberg, R.A., 2009. The basics of epithelial-mesenchymal transition. J. Clin. Invest. 119 (6), 1420–1428.

Pang, A., Carbini, M., Moreira, A.L., Maki, R.G., 2018. Carcinosarcomas and related cancers: tumors caught in the act of epithelial-mesenchymal transition. J. Clin. Oncol. 36 (2), 210–216.

Quddus, M.R., Sung, C.J., Lauchlan, S.C., 2000. Benign and malignant serous and endometrioid epithelium in the omentum. Gynecol. Oncol. 75, 227–232.

Ren, F., Wang, D., Jiang, Y., Ren, F., 2012. Epigenetic inactivation of hMLH1 in the malignant transformation of ovarian endometriosis. Arch. Gynecol. Obstet. 285 (1), 215–221.

Shaco-Levy, R., Piura, B., 2008. Endometrioid endometrial adenocarcinoma recurring as carcinosarcoma. J. Obstet. Gynaecol. Res. 34 (2), 279–282.

Slavin, R.E., Krum, R., Van Dink, T., 2000. Endometriosis-associated intestinal tumors: a clinical and pathological sturdy of 6 cases with a review of the literature. Hum. Pathol. 31, 456–463.

Stewart, C.J.R., McCluggage, W.G., 2013. Epithelial-mesenchymal transition in carcinomas of the female genital tract. Histopathology 62, 31–43.

Wells, M., Oliva, E., Palacios, J., Prat, J., 2014. Mixed epithelial and mesenchymal tumors. In: Kurman, R.J., Carcangiu, M.L., Herrington, C.S., Young, R.H. (Eds.), WHO classification of tumours of female reproductive organs. International Agency for Research on Cancer, Lyon, pp. 150–151.