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Case report

Mucinous adenocarcinoma of the endometrium with metastasis to the clitoral glans after pelvic exenteration for radiation resistant vaginal cuff recurrence

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ABSTRACT

Mucinous adenocarcinoma of the endometrium (MACE) is a rare subtype of endometrial adenocarcinoma that often presents a significant diagnostic challenge due to its variation from the conventional morphologic appearance of endometrioid epithelium. This case report is of a woman who has survived 4 years after pelvic exenteration and subsequent vulvectomy for recurrent MACE.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy with over 63,000 new cases reported annually in the United States. MACE is an unusual variant of endometrial adenocarcinoma, comprising only 1–9% of all endometrial adenocarcinomas. It is defined as adenocarcinoma of the endometrium showing more than 50% mucinous differentiation. This mucinous differentiation is usually endocervical-like in type, but rare cases have shown intestinal-type mucinous differentiation. The clinical features are similar to those of typical endometrioid adenocarcinoma, including an association with hyperestrogenism. Most patients with MACE present with low grade disease (Rauh-Hain et al., 2016) at an early stage (Jalloul et al., 2012), and the outcome for such patients is excellent when treated with surgery alone (Jalloul et al., 2012). Although patients with MACE are more likely to have pelvic lymph node involvement, survival rates are not significantly different than for endometrioid adenocarcinoma (Rauh-Hain et al., 2016). Recurrences in MACE are more likely in cases presenting at an already advanced stage, with deep myometrial invasion, involvement of the lower uterine segment, or with higher grade tumors (Jalloul et al., 2012). These recurrent tumors present as multifocal disease, with only a few cases of isolated recurrence. Patients with isolated recurrence are ideal for pelvic radiation therapy and pelvic exenteration (Morris et al., 1996).

Pelvic exenteration is a radical gynecologic surgery that involves the removal of the uterus, cervix, vagina, bladder, and rectum – with most cases involving the removal of some or all of these organs. The indications for this surgery includes; persistent disease after previous treatment with surgery or radiation, confinement of disease to the central pelvis with no distant metastasis indicating the possibility of complete resection, and involvement of the rectum or bladder in which other treatment options might result in the formation of a fistula (Shingleton et al., 1989).

2. Case presentation

A 58-year-old woman gravida 1, para 1, with grade 1 endometrial cancer on D&C had a robotic assisted hysterectomy, bilateral salpingoophorectomy and pelvic node dissection in January of 2010. The final pathology on the uterus was only complex hyperplasia of the endometrium with atypia, with no evidence of residual adenocarcinoma. In December 2012, she presented with abnormal bleeding. A PET scan identified a 3 × 4 cm lesion at the vaginal cuff. This was biopsied at an outside institution and diagnosed as moderately differentiated (Grade 2) intestinal-like mucinous adenocarcinoma. Gastroscopy and colonoscopy were performed and showed no evidence of upper or lower gastrointestinal malignancy. Her CEA was 0.7 and CA19–9 was 9. She received external beam radiation therapy up to 50 Gy with additional treatments of vaginal brachytherapy up to 15 Gy from January to March of 2013. She did not receive any chemotherapy.

Seven months after the radiation therapy she had a persistent cavitary lesion at the vaginal apex, and a repeat PET scan showed FDG focus at the vaginal cuff, with no nodal disease or metastasis noted. This was biopsied and diagnosed again as moderately differentiated mucinous adenocarcinoma. Immunohistochemical stains performed on the biopsy material showed the tumor cells were positive for cytokeratin 7

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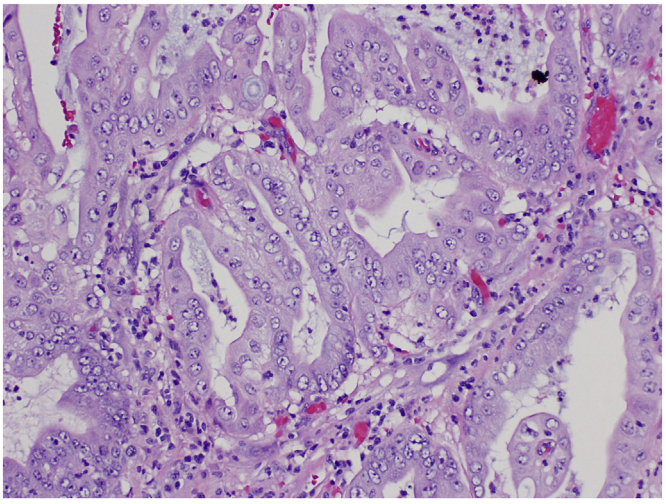

Fig. 1. The tumor consists of columnar cells with eosinophilic or vacuolated cytoplasm and occasional goblet cells, characterized by a circular apical inclusion of blue mucin. There is loss of nuclear polarity and areas of nuclear crowding. The nuclei themselves are round to oval with vesicular chromatin and some prominent nucleoli. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and CDX2, focally positive for cytokeratin 20, and negative for ER, PR and PAX-8, an immunophenotype consistent with intestinal-type

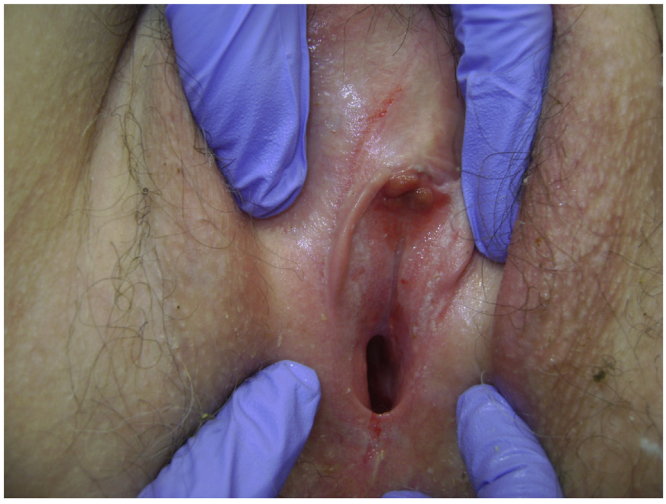

Fig. 3. Photograph of the clitoral recurrence lesion.

mucinous differentiation. She then underwent a total pelvic exenteration including total vaginectomy, low rectal resection and anastomosis, continent urinary diversion using the right colon, diverting loop ileostomy with omental J flap pedicle, and complete left pelvic node dissection. The resected specimen showed an exophytic mass measuring 4.5 by 3.7 by 1.9 cm located in the vaginal wall and adherent to, but not invading into the bladder wall anteriorly. There was no involvement of

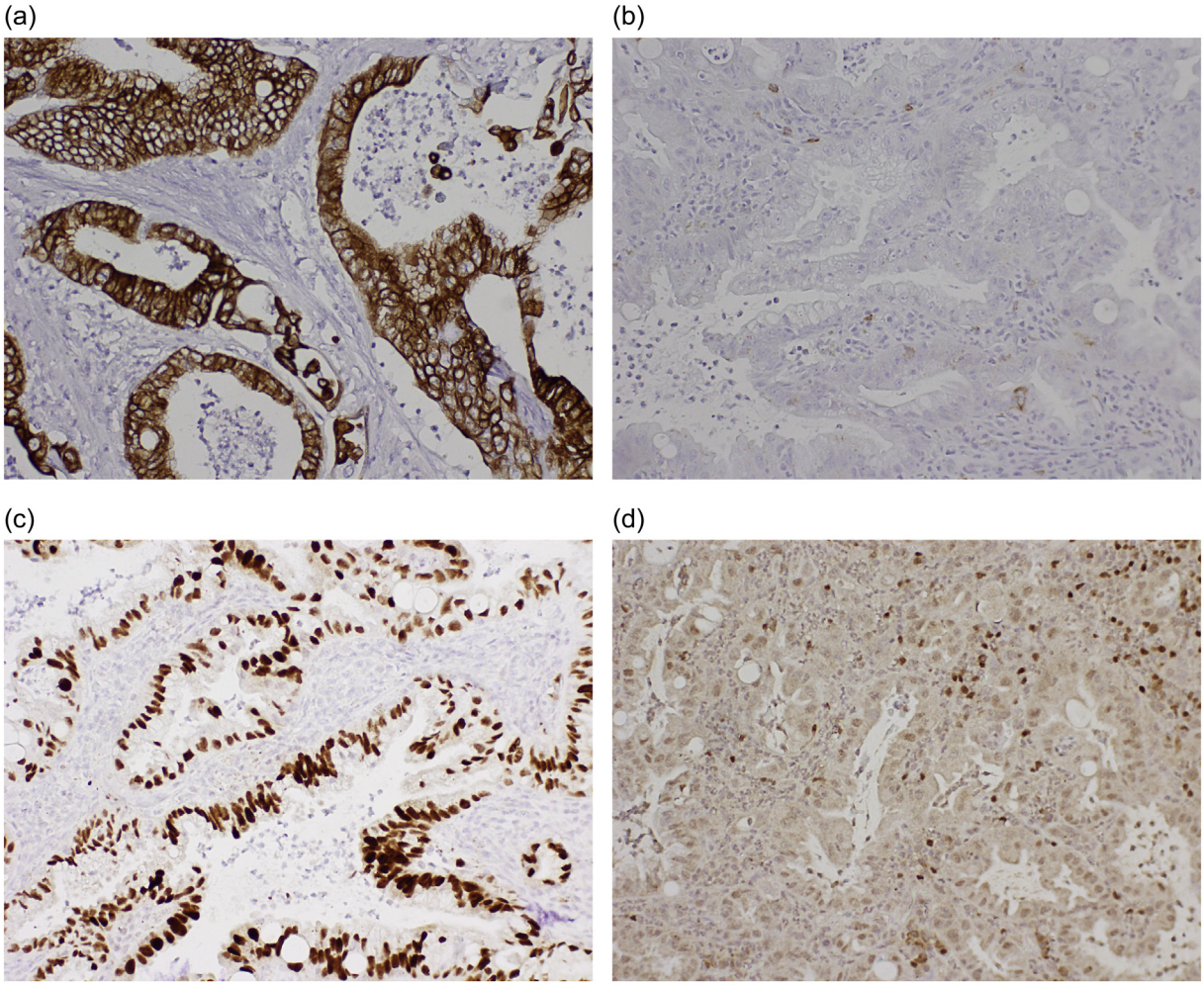

Fig. 2. The tumor cells are positive for cytokeratin 7(a), negative for cytokeratin 20 (b), positive for CDX2 (c) and negative for PAX8.

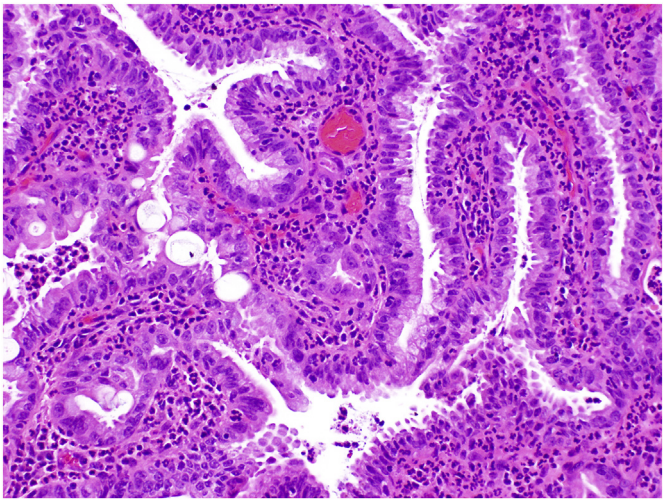

Fig. 4. The clitoral recurrence shows similar morphology to the prior vaginal recurrence.

the rectal wall, and all margins of resection were free of tumor. Microscopic examination of the tumor showed moderately differentiated mucinous adenocarcinoma with goblet cells, consistent with intestinal-type mucinous differentiation (Fig. 1). Immunohistochemical staining was similar to the previous biopsy, showing positivity for cytokeratin 7 and CDX2 and negativity for PAX-8, but with virtually no react for cytokeratin 20 (Fig. 2).

Six months after the pelvic exenteration surgery, she had another recurrence in the clitoris (Fig. 3) A biopsy confirmed this as a mucinous tumor consistent with her prior lesions. A radical vulvectomy was performed to remove the clitoris and the remaining vulva. The resected specimen showed a focus of mucinous adenocarcinoma with goblet cells confined to the mucosa of the glans clitoris with no involvement anywhere else in the vulva (Fig. 4). Immunohistochemical stains showed a pattern identical to the vaginal tumor recurrence excised previously.

After 4 years of surveillance, the patient has no evidence of disease.

3. Discussion

MACE is an uncommon variant of endometrial carcinoma, and a presentation with prominent intestinal-like mucinous differentiation, as seen in this case is exceptionally rare. Intestinal- type mucinous differentiation has been described in rare cases of both benign and malignant endometrial lesions (Buell-Gutbrod et al., 2013; Park et al., 2009; McCluggage et al., 1995; Nicolae et al., n.d.). In most reported cases; the intestinal-type differentiation has been detected only by expression of enteric-type mucins (McCluggage et al., 1995) or immunohistochemical positivity for cytokeratin 20, CDX2 or both (Park et al., 2009), without the development of goblet cell morphology. The presence of goblet cell morphology in endometrial lesions is so unusual, in fact, that the finding raises a strong suspicion for metastasis, particularly from a gastrointestinal origin. While the retention of cytokeratin 7 positivity in intestinal-type mucinous differentiation of the endometrium will mitigate against colorectal origin, as the typical immunophenotype of colorectal epithelium is cytokeratin 7 negative and cytokeratin 20 positive, the immunophenotype of intestinal type mucinous metaplasia in the endometrium is identical to that which may be seen in tumors of upper digestive tract and pancreas, and careful clinical correlation must be undertaken to ensure the absence of such a lesion before making a definitive diagnosis of a gynecologic primary. The expression of PAX8, a marker of Mullerian origin, has not, to our knowledge, been evaluated in any other cases of MACE. Its expression would have been reassuring to confirm the endometrial origin of the tumor, but the significance of the lack of expression in this case is not clear given the absence of data in this type of aberrant differentiation.

Despite the relative rarity of MACE compared to the typical endometrioid morphology of endometrial adenocarcinoma, there appears to be no significant difference in clinical behavior or survival for tumors of this morphology. This appears to include the association with estrogen-driven hyperplasia of the endometrium, which has been reported in previous cases like of Buell-Gutbrod et al. and Nicolae, A et al., and was identified in this case as well. The extremely unusual clinical behavior of the case reported here, in which the tumor was initially diagnosed on endometrial biopsy, was absent in the subsequent hysterectomy, and recurred as separate isolated lesions in both the vaginal cuff and the glans clitoris, is difficult to explain. There are too few cases of MACE with such intestinal-type differentiation reported to date to determine if this very unusual morphology portends a different prognosis from the more common endocervical type of mucinous morphology. It is well known, however, that for endometrial adenocarcinoma of conventional type, a higher grade at diagnosis is an independent risk factor associated with a higher risk of recurrence, which appears to be true for MACE as well(Jalloul et al., 2012), making the higher grade of the tumor (Grade 2) the most likely explanation for the course of disease in this patient. It remains unclear if the exposure to radiotherapy might have had any effect on the tumor morphology or behavior in the recurrent vaginal and vulvar lesions.

The use of chemotherapy is recommended for treatment of metastatic disease, with radiation therapy indicated for local pelvic management of metastatic recurrences. Pelvic exenteration surgery can be used as a potentially curative option in patients that have recurrence after prior radiation therapy (Shingleton et al., 1989).

4. Conclusion

Pelvic exenteration and subsequent vulvectomy was successful in treating this patient with unusual metastasis of mucinous cancer of the endometrium.

Author contribution

O.M prepared the manuscript, searched the literature.

E.K, D.R are both responsible for the pathology report and imaging.

K·H is the principal investigator and surgeon on this case. Also participated in manuscript preparation.

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