

The similarities and differences between mesonephric carcinoma and mesonephric-like carcinoma: Two cases

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1. Introduction

Mesonephric carcinomas are rare cancers of the gynecologic tract that are thought to arise from mesonephric remnants. Although these lesions are uncommon, with associated mesonephric hyperplasia, location (lateral aspects of the deep cervical tissue or adnexa), and diagnostic histological findings, the diagnosis is straightforward. Even rarer, and more recently discovered, are mesonephric-like carcinomas of the ovary and uterine corpus. These entities are not considered to be derived from mesonephric epithelia but have histologic and molecular similarities to mesonephric carcinoma, likely representing mesonephric differentiation (Howitt and Nucci, 2018).

Here we describe two cases at our institution, one of mesonephric carcinoma of the uterine corpus and one of mesonephric-like carcinoma of the ovary, and discuss the issues related to arriving at a definitive diagnosis and tumor staging.

2. Patient #1

The first patient was a 63-year-old female who presented with acute lower abdominal pain. A pelvic ultrasound demonstrated a cystic and solid mass within the uterus and an MRI demonstrated hemorrhagic

material in the posterior myometrial wall. This was initially thought to be an abscess secondary to sigmoid disease given known diverticulosis diagnosed after a colonoscopy five years prior, which was otherwise benign. Her past surgical history included an endometrial ablation over 10 years prior. She received regular gynecologic care and had a recent normal Pap smear. Given the imaging findings, the patient had a consultation with colorectal surgery and underwent follow-up imaging with a CT abdomen/pelvis which demonstrated multiple masses in the uterus not associated with ascites and not connected to otherwise normal rectum. There were mild changes of diverticulosis noted with no evidence of diverticulitis or abscess formation. An 8 mm nodule at the right lung base, as well as a small left adrenal gland adenoma were noted. The patient underwent a diagnostic laparoscopy and lysis of adhesions that demonstrated filmy adhesions from the rectosigmoid to the right posterior aspect of the uterus with mild amount of inflammation noted in the posterior cul-de-sac, diverticula noted at the proximal sigmoid colon, and a grossly normal uterus, tubes and ovaries bilaterally. Given the normal findings, the patient returned to routine gynecologic care.

She re-presented two years later with worsening lower abdominal pain. CT imaging demonstrated an 8.1 × 8.5 × 6.9 cm heterogeneous mass seen posterior to the bladder, in the region of the uterus that was

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considered not typical of a fibroid uterus as well as a 10.0 × 8.4 mm nodule in the right middle lobe. Surgery was recommended and she underwent an exploratory laparotomy, radical hysterectomy with bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy. Intraoperative findings included a large globular uterus extending to the bilateral pelvic sidewalls, visible varicosities of the uterine serosa posteriorly, and the plane between the bladder and uterus was obliterated with concern for invasion although no visible tumor was seen in this plane. There was minimal normal residual cervical tissue as the cervix appeared attenuated with growth of the mass. The ureters bilaterally were adherent to the mass with no evidence of ascites, metastatic disease, or suspicious lymphadenopathy. Intraoperative pathology demonstrated adenocarcinoma, suspicious for endometrioid type.

Gross examination of the uterus and cervix revealed a uterine corpus-based 8.5 × 5.8 × 5.7 cm hemorrhagic and necrotic mass limited to the myometrium that was extending into the lower uterine segment. The endometrium, cervix, uterine serosa, fallopian tubes, and ovaries were unremarkable. Microscopic examination of the uterine mass revealed a moderately differentiated adenocarcinoma (Fig. 1). The tumor cells formed variable size nodules that infiltrated myometrium. The carcinoma cells were arranged in tubular glands lined by mucin-free glandular epithelium. Other patterns, including papillary and spindle cell patterns, were also present. By immunohistochemistry, tumor cells were positive for GATA3 (strong nuclear staining) and negative for estrogen receptor (ER). The histologic and immunohistochemical features indicated mesonephric differentiation. No mesonephric remnants were

identified in the entirety of cervical tissue submitted. No definite endometriosis was identified. The tumor was not entirely located in the cervix, but very close to it in the myometrium of the lower corpus and lower uterine segment. Nineteen pelvic lymph nodes were benign. As mesonephric carcinomas are commonly identified in the cervix, pathology favored to stage it as a primary cervical mesonephric carcinoma (FIGO IIA2). At our institution's multidisciplinary Tumor Board, pelvic radiation with sensitizing cisplatin was recommended. The patient completed six cycles of pelvic radiation with sensitizing cisplatin. She is currently undergoing surveillance and has been without evidence of disease for almost two years. A post-treatment CT scan demonstrated two postoperative lymphoceles at the location of the lymph node dissection, one of which has since resolved.

3. Patient #2

The second patient was a 67-year-old female who presented with a pelvic and omental mass on CT abdomen/pelvis after a year of right lower quadrant pain with associated nausea, bloating, and unintentional weight loss. Her past medical history included sarcoidosis, diabetes, and hypertension. CT demonstrated a small right pleural effusion, a complex predominantly cystic mass along the right side of the small bowel mesentery suspicious for a metastatic deposit, and a similar but slightly smaller mass in the right adnexal region which could correspond to a primary ovarian lesion. She had a fibroid uterus and bilateral inguinal and retroperitoneal adenopathy. CA-125 was 19 and HE4 was 277

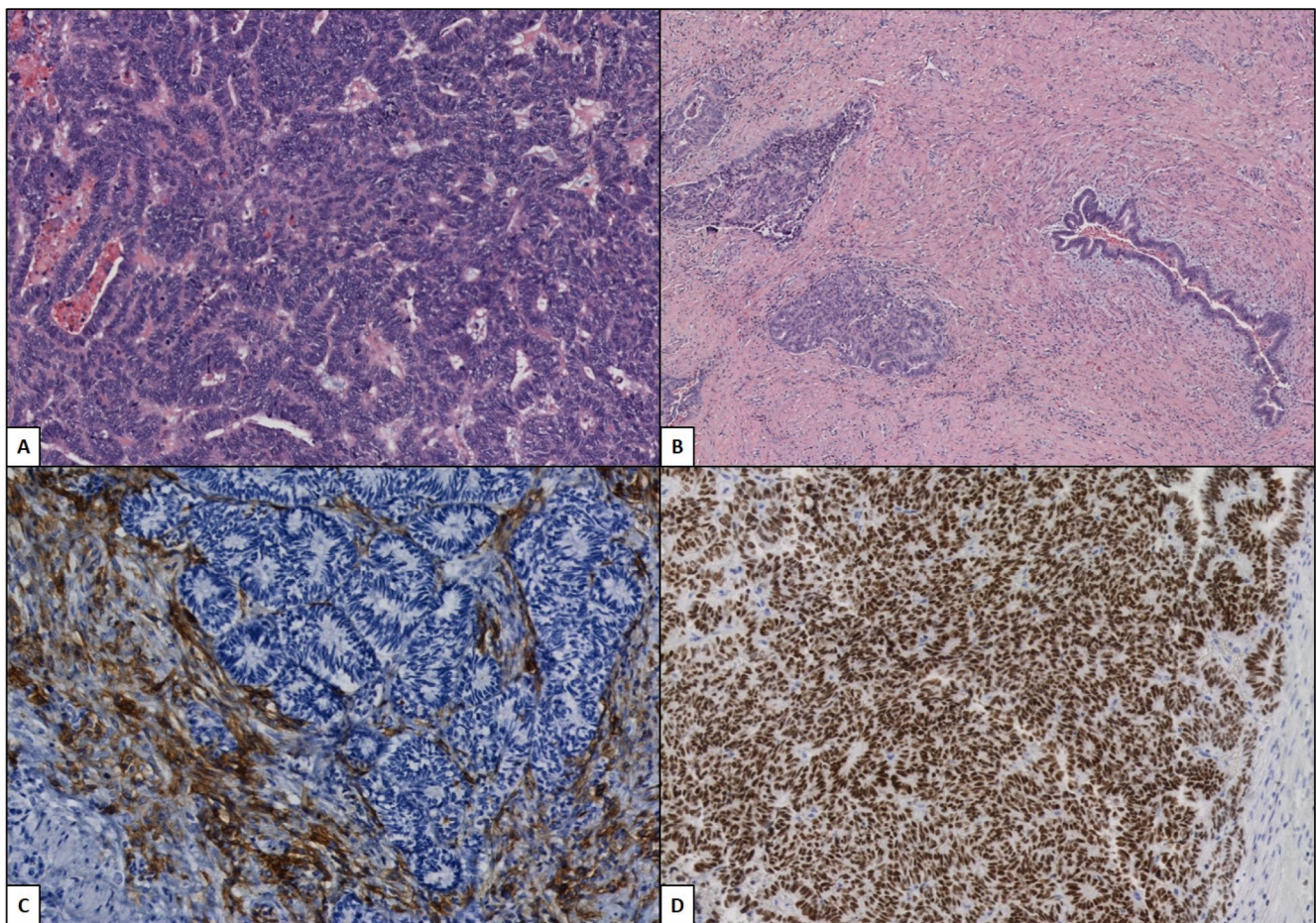


Fig. 1. The microscopic examination of the uterine mass revealed a moderately differentiated adenocarcinoma. The tumor cells formed variable size nodules that infiltrated myometrium. The carcinoma cells were arranged in tubular glands lined by mucin-free glandular epithelium. Other patterns, including papillary and spindle cell patterns, were also present. By immunohistochemistry, tumor cells were positive for GATA3 (strong nuclear staining) and negative for estrogen receptor (ER).

giving her a high-risk ROMA score of 48%. The patient underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and right para-aortic lymph node biopsy.

A 12 × 8 × 5 cm right adnexal mass was identified during intra-operative evaluation. The frozen section from the mass was diagnosed as “high-grade Mullerian adenocarcinoma.” The gross examination of formalin-fixed tissue revealed a solid and cystic right adnexal mass involving the right ovary and right side of the uterus. The cervix, uterine serosa, right fallopian tube, left fallopian tube, and ovary were grossly unremarkable. The microscopic examination revealed an adenocarcinoma arising in a setting of endometriosis. The tumor was high-grade and displayed areas of moderate to poorly differentiated adenocarcinoma tumor cells that were arranged in a variety of architectural patterns including tubular, retiform, solid, papillary and spindle cell patterns (Fig. 2). Tumor involved a right ovarian endometriotic cyst, right uterine serosa, full thickness myometrium and endometrium. Eosinophilic hyaline secretions were present in the glandular lumina. Hyperplastic mesonephric remnants were also identified in the para-ovarian tissue. By immunohistochemistry, tumor cells were positive for GATA3, negative for estrogen and progesterone receptors, negative for TTF-1, positive for mismatch repair proteins, and showed wild-type p53 staining. There was evidence of atypical endometrial hyperplasia of the endometrium and adenomyosis. The right para-aortic lymph node was positive for adenocarcinoma. The omentum and peritoneal fluid were negative for carcinoma. The tumor was diagnosed as FIGO IIIA mesonephric-like adenocarcinoma (high-grade) of the ovary.

The patient was presented at our institution’s multidisciplinary Tumor Board and chemotherapy was recommended. She underwent six cycles of carboplatin, paclitaxel, and bevacizumab and completed 22 cycles of bevacizumab maintenance therapy. Prior to cycle 9 of maintenance therapy, a CT scan demonstrated a mesenteric mass, thought to be a fluid collection, that was stable. After 22 cycles of maintenance treatment, the patient was considered to have a complete response. Over six months into surveillance, she had a rising CA-125 level from baseline of 34 unit/mL to 60 unit/mL. A CT scan demonstrated interval enlargement of a solitary pulmonary nodule in the right lung base measuring 9 mm concerning for progression of disease. The mesenteric mass previously seen was stable in size. She was started on carboplatin and Doxil, most recently completing her sixth cycle. There was an interval decrease in the size of the pulmonary nodule to 5 mm on most recent CT scan.

4. Discussion

These two clinical cases highlight two rare gynecologic cancer types that share key similarities yet are considered distinct entities. How we choose to categorize them may have direct implications on treatment and prognosis.

Mesonephric carcinomas (MC) are defined based on location and classical histologic findings. These commonly arise from the lateral wall of the cervix. Mesonephric remnants or hyperplasia are putative precursors that, if present, are diagnostic of mesonephric carcinoma. However, they may not be identified or present in association with the

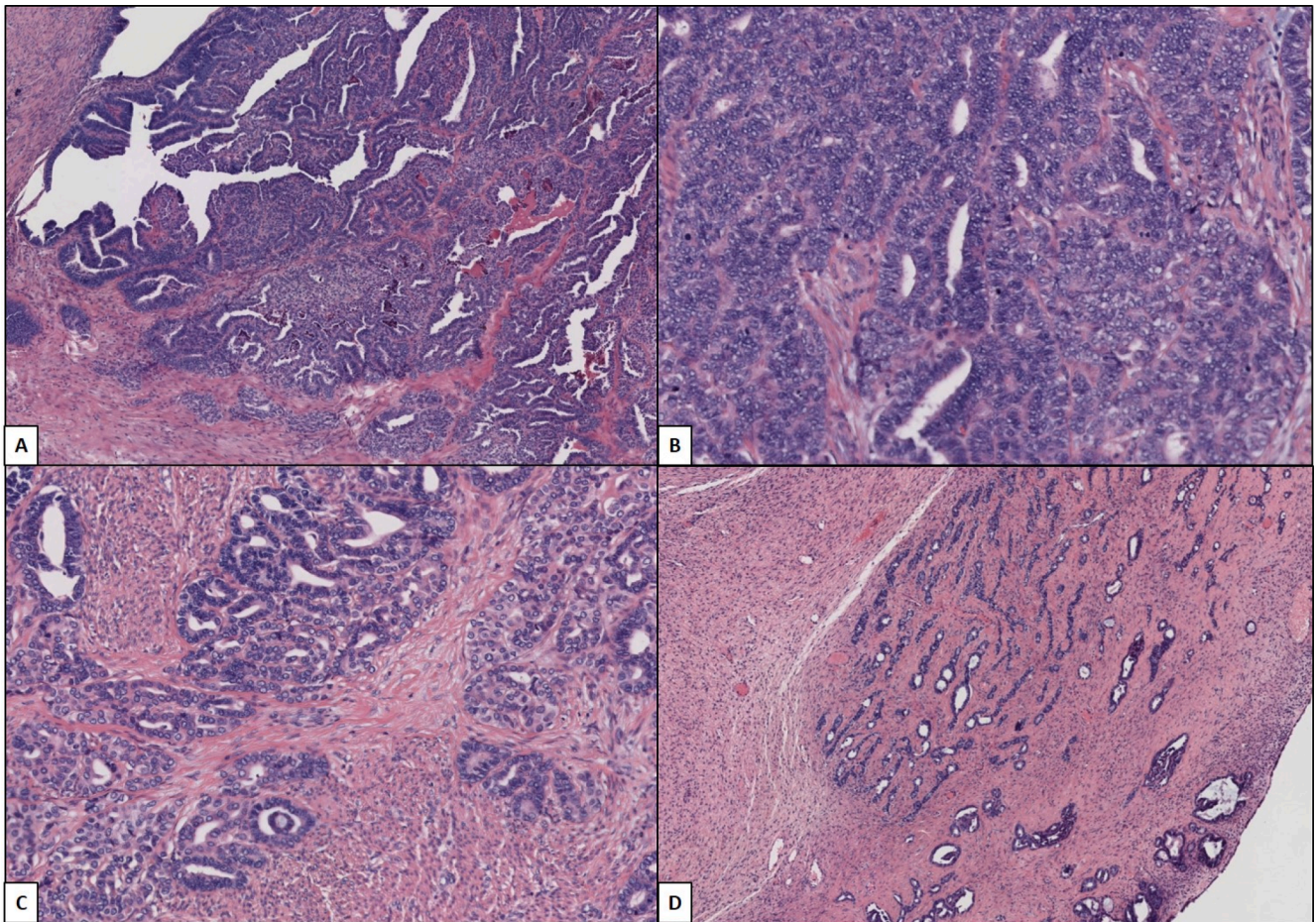


Fig. 2. The microscopic examination revealed an adenocarcinoma arising in a setting of endometriosis. The tumor was high-grade and displayed areas of moderate to poorly differentiated adenocarcinoma tumor cells that were arranged in a variety of architectural patterns including tubular, retiform, solid, papillary and spindle cell patterns.

lesion (Howitt and Nucci, 2018). MC are a rare variant of non-HPV related cervical adenocarcinoma, representing <1% of all cervical carcinomas, and can be clinically aggressive (Howitt and Nucci, 2018). Less commonly, MC can be found in the vagina or myometrium. The first reported case of uterine corpus MC was published in 1995 and since then, 30 cases have been reported in the literature (Zhang et al., 2019). Our first case adds to this body of literature.

Mesonephric-like carcinomas (MLC) are histologically similar to MC, and often clinically indistinguishable from other endometrial or epithelial ovarian malignancies (Howitt and Nucci, 2018). However, MLC are thought to originate from the Mullerian tract, are most commonly associated with the endometrium, and are not associated with any mesonephric remnants or hyperplasia. Only 40 cases of endometrial MLC have been reported in literature. Ovarian MLC are even more uncommon and were first described in the literature by McFarland et al in 2016 (McFarland et al., 2016). To date, there have been only 17 cases, four of which are unpublished (McCluggage et al., 2020) (Table 1). We believe our second patient case to be the 18th described case of an ovarian MLC (McFarland et al., 2016; McCluggage et al., 2020; Chapel et al., 2018; Kezlarian et al., 2019; Dunder, 2020; Seay et al., 2020; Chen et al., 2020). Similar to previous reports, our patient's tumor was found in tandem with an endometriotic cyst within the same ovary. Including our case, 13 of the 16 cases reporting associated findings have other pathological findings in the same ovary: six of those had evidence of endometriosis (McCluggage et al., 2020).

MC and MLC show overlap in histological findings. Both often have a combination of different growth patterns: tubular, glandular, papillary, retiform, and spindle. They are immunohistochemically characterized by GATA3, calretinin, and CD10 positivity; as well as wild-type p53 expression and estrogen-receptor/progesterone-receptor negativity. Molecularly, both cancers are associated with KRAS mutations and microsatellite stability (Kolin et al., 2018). While both patients experienced complete response after initial adjuvant treatment, there may be a role of targeted immunotherapy based on KRAS mutations and is an area that warrants further investigation (Lin et al., 2020).

A consensus was made in our second case to consider the lesion FIGO IIIA ovarian MLC based on the intimate association of the lesion with an endometriotic cyst within the ovary given the previously described relationship between MLC of the ovary and endometriosis (McFarland et al., 2016; McCluggage et al., 2020). Although the same tumor had evidence of focal hyperplastic mesonephric remnants and myometrial involvement, classic features of MC, these were noted in the paraovarian and outer myometrial tissue making staging of the primary ovarian lesion more difficult. There is little to no literature on a primary ovarian MC.

Both of these tumor types may not follow typical tumor staging criteria or pattern. Staging of cervical carcinoma is based on the premise that cervical epithelial malignancy starts in the cervical mucosa and the depth of the tumor determines the T stage. In mesonephric carcinoma, the tumor often originates in the cervical fibromuscular wall (not in the mucosa); therefore, if staged like conventional cervical carcinoma it would often be considered advanced stage. Our first case demonstrates the challenge of staging these tumors, particularly when they arise away from the cervical or endometrial lining. In determining staging, the options considered were FIGO Stage IB primary uterine mesonephric carcinoma or FIGO stage IIB cervical mesonephric carcinoma. Ultimately, after review by our multidisciplinary Tumor Board, cervical tumor staging was preferred. Similarly MLC of the uterus may not start in the endometrium but rather most of the tumor density may be in the myometrium. The tumor location may also depend on the presence of endometriosis. In our second case, although mesonephric remnants were identified, the endometriosis and atypical endometrial hyperplasia were also noted in the paraovarian and outer myometrial tissue suggesting that the tumor actually arose in the myometrium/paraovarian tissue from endometriosis. This renders organ/tissue based T staging in these cases extremely difficult.

Table 1

Literature review of mesonephric-like carcinoma of the ovary.

Case	Age	FIGO Staging	Ovary	Associated Findings
1–5 (McFarland et al., 2016)	42–72	IA (3), IB (1), IIC (1)	Left (2), bilateral (2), unknown (1)	Endometriosis (3); none (2)
6 (Chapel et al., 2018)	80	Not reported	Right	Serous borderline tumor and low-grade serous carcinoma
7 (Pors et al., 2018)	67	IC	Not Reported	Not reported
8–9 (Kezlarian et al., 2019)	36–45	III (1), IIIA (1)	Right (1), Left (1)	Not reported
10 (McCluggage et al., 2020)	61	IIIA1	Left	Serous borderline tumor (low-grade serous carcinoma in extraovarian tissues)
11–14 (McCluggage et al., unpublished) ^a	60–73	Not reported	Right (1), Left (2), unknown (1)	Borderline endometrioid adenofibroma, endometriosis (1); mixed serous and mucinous cystadenoma (1); none (1); serous cystadenoma (1)
15 (Dunder, 2020)	61	IV	Left	Serous borderline tumor
16 (Seay et al., 2020)	67	IA	Right	Endometriosis
17 (Chen et al., 2020)	29	IC	Right	none
18 (Current)	67	IIIA	Right	Endometriosis

^a Cases 11–14 were mentioned in McCluggage et al. (2020), but were not formally presented.

While much progress has been made in attempting to clarify classification schema of these cancers, these cases demonstrate the inherent ambiguity that exists along the spectrum of mesonephric and mesonephric-like neoplasms of the female genital tract. Additional detailed accounts will provide more data points for how best to classify, stage, and potentially, how to treat these malignancies.

Informed consent

Written informed consent was obtained from the patients 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.

Author contributions

A Kulkarni, A Chiem made contributions to conceptualization, data curation, drafting and revising the manuscript. K Singh made contributions to pathology analysis and drafting the manuscript. C. Mathews, P. DiSilvestro, L. Beffa made contributions to supervision, conceptualization, drafting and revising the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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