



## Case report

## Two sisters with Mayer-Rokitansky-Küster-Hauser syndrome and serous adenocarcinoma of the ovary

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## A B S T R A C T

**Background:** Mayer-Rokitansky-Küster-Hauser syndrome is a rare entity with proposed genetic underpinnings. Ovarian carcinoma has well-described genetic associations and syndromes, although much of the etiology of the disease remains unknown.

**Cases:** Two sisters present in the 1970s with primary amenorrhea, 46, XX karyotypes, and absent uteri consistent with MRKH syndrome. In the 2010s, both sisters again present for care. Case 1 presents one sister with stage IIIC serous ovarian adenocarcinoma and negative BRCA panel. Case No 2 presents the other sister with stage IIIC serous ovarian adenocarcinoma and a negative panel for 32 genetic variants associated with ovarian carcinoma.

**Conclusion:** The familial association of two rare diseases and negative genetic workup could point to a new genetic understanding of reproductive structure development and ovarian carcinogenesis.

## 1. Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a well-described entity occurring in approximately 1:5000 female births. In MRKH, the müllerian duct system forms incompletely during fetal development, leading to congenital absence of the upper one-third vagina and variable uterine development with preserved ovarian function and normal female secondary sex characteristics. Despite the clinical definition of the syndrome, the underlying etiology remains unclear. After several case reports of familial occurrences of MRKH syndrome (Jones and Mermut, 1972; Griffin et al., 1976), Griffin et al. (Griffin et al., 1976) postulated that the syndrome may have an underlying genetic basis, and both Griffin and Guerrier (Guerrier et al., 2006) postulated that MRKH syndrome may represent a genetic defect with incomplete penetrance and variable expressivity. Multiple studies have searched for candidate genes, and a clinical trial in France (NCT02967822) is currently recruiting patients with MRKH syndrome to elucidate the genetic and molecular makeup of the syndrome, but at this point a definitive genetic explanation has not been reached. One of the original case reports of familial occurrence of MRKH by Jones and Mermut (Griffin et al., 1976) reported on two sisters who both presented with primary amenorrhea and were found to have absent vaginal cavities with normal breast development and pubic hair distribution.

Karyotyping revealed 46,XX genotype in both sisters. On laparotomy, each sister had small or absent Müllerian tissue consistent with Mayer-Rokitansky-Küster-Hauser syndrome with benign ovarian biopsies at the time of surgery. Analysis of the probands' pedigree failed to identify an obvious genetic etiology. Subsequently, the two sisters described in the Jones and Mermut report developed serous adenocarcinoma of the ovary, and we describe their ovarian cancer courses below. Although multiple genetic mutations have been associated with ovarian cancer, most cases have no identifiable genetic cause. There are no previous descriptions of familial occurrences of both MRKH syndrome and ovarian cancer. Thus, this case of two sisters could indicate a yet-unknown variant that explains anomalous development of multiple female reproductive structures.

## 2. Cases

## 2.1. Case No. 1

A 64 year old Caucasian gravida zero presented in July 2014 with abdominal bloating and ultrasound-confirmed ascites. A computed tomography (CT) scan of the abdomen and pelvis additionally demonstrated nodularity and thickening concerning for carcinomatosis, a 6.9 × 4.6 cm lobulated liver lesion at the level of the hepatic dome, a

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5.8 × 4.1 cm left ovary with a large cystic component, and an absent uterus. Her past medical history is notable for MRKH syndrome, hypertension, hyperlipidemia, osteoarthritis, anxiety, hiatal hernia, and tonsillectomy. She is a former smoker with an eight pack-year smoking history and she drinks socially. Physical exam was notable for normal external genitalia with a short vagina, absent cervix/uterus, and no palpable masses. She underwent paracentesis in July 2014 with ascites positive for adenocarcinoma (CK7 +/Ca-125 +/WT-1 +, CK20-/CDX-2-/ER-/calretinin-) as well as fine needle aspiration biopsy of a left omental mass, also with pathology consistent with high-grade serous adenocarcinoma (EMA +/Ca-125 +/WT-1 +/calretinin-). Her initial cancer antigen 125 (Ca-125) in August 2014 was 1510. She completed three cycles of neoadjuvant chemotherapy with paclitaxel, carboplatin, and bevacizumab (third cycle of bevacizumab held) with a Ca-125 of 31 at completion of this regimen. In October 2014, she underwent an exploratory laparotomy, bilateral salpingo-oophorectomy, and omentectomy for optimal cytoreduction to no gross residual disease. Surgical pathology was consistent with stage IIIC, high-grade serous adenocarcinoma involving the left ovary and fallopian tube without lymphovascular invasion. Post-operatively, she received four additional cycles of paclitaxel and carboplatin with additional cycles held after an admission for sepsis secondary to a neck abscess. The patient had neuropathy and leg cramping secondary to her chemotherapy. She had genetic testing in January 2016 with no mutation detected in the BRCA1/BRCA2 genes and no BART rearrangement. The patient has since been under routine surveillance with no evidence of disease for 21 months.

## 2.2. Case No. 2

The 63 year old Caucasian gravida zero sister of the woman in Case 1 presented for gynecologic oncology care at a separate institution in September 2015 with bloating and abdominal discomfort, with an ultrasound demonstrating abdominal ascites and an initial Ca-125 of 159. Her past medical history is notable for MRKH syndrome and right salpingo-oophorectomy for a 15 cm ovarian cyst, basal cell skin cancer s/p removal, hypercholesterolemia, two childhood hernia surgeries, sebaceous cyst removal, and tonsillectomy. She is a non-smoker and has never used oral contraceptive pills (OCPs). The physical exam was notable for mild abdominal bloating with no fluid wave. A CT scan demonstrated omental nodularity and caking, free pelvic fluid, mildly enlarged bilateral external iliac and inguinal lymph nodes, and an absent uterus. Repeat Ca-125 was 209. The patient had genetic screening through Ambry Genetics' 32-gene panel of mutations associated with hereditary cancers [Table 1] with no clinically significant variants detected. The patient underwent an exploratory laparotomy; operative findings included diffuse carcinomatosis and omental caking, tumor nodularity along the peritoneum and omentum, and absent uterus. She

was optimally cytoreduced to no disease > 1 cm (including left salpingo-oophorectomy, omentectomy, and argon beam coagulation of pelvic and diaphragmatic implants). Pathology demonstrated stage IIIC, grade 3 serous tubal intraepithelial carcinoma without lymph-vascular invasion. She then underwent six cycles of every three week (q3 week) 120 mg intravenous (IV) docetaxel/120 mg intraperitoneal (IP) cisplatin and q3week 102 mg IP paclitaxel chemotherapy with pegfilgrastim support, which she tolerated well except for neuropathy treated with gabapentin. She had a normal CT scan and non-measurable Ca-125 after 4 cycles. She remained with no evidence of disease for 11 months until February 2017, when she developed nausea, bloating, and weight loss. There was pelvic nodularity felt on exam, a repeat Ca-125 was elevated at 20, and a CT scan demonstrated recurrent ovarian cancer with moderate volume ascites, diffuse peritoneal enhancement, and peritoneal nodularity. The team has recommended carboplatin, bevacizumab, and gemcitabine chemotherapy to treat her recurrence.

## 3. Discussion

To our knowledge, this is the first reported case of the familial occurrence of both MRKH syndrome and ovarian cancer. Ovarian carcinoma is the eighth most common cancer found in females in the United States, with 11.9 new cases/100,000 women each year and high disease-specific mortality (Cancer Stat Facts, 2017). Nulliparity, obesity, endometriosis, and family history significantly increase the risk of ovarian cancer, while the use of OCPs and a history of tubal ligation significantly decrease the risk, although the specific risks vary by histologic subtype (Pearce et al., 2013; Pearce et al., 2015; Wentzensen et al., 2016; Auranen et al., 1996). Interestingly, both women in this case report were nulliparous, increasing their baseline risk. The patient in Case No. 2 had never used OCPs, although she previously underwent unilateral salpingo-oophorectomy. Ovarian cancer has long been known to have a genetic component, with 10–18% of all ovarian carcinomas associated with mutations in multiple genes including BRCA1/BRCA2, mismatch repair genes (MLH1, MLH3, MSH2, MSH6, TGFBR2, PMS1, PMS2), PTEN, STK11, and TP53, and a growing list of identifiable affected pathways including PI3K signaling, the WNT pathway, the mTOR pathway, and the hypoxia pathway (Krzystyniak et al., 2016). In our cases, the two sisters underwent genetic screening that was negative as described above. Both sisters had high-grade serous carcinoma on pathology, which is associated with activating mutations in TP53 (in over 90% of cases), BRCA1/2 mutations, and homologous repair effector inactivations (in 20% of patients with HGSC overall but almost 50% of late-stage serous ovarian carcinomas) (Krzystyniak et al., 2016). There are several possible explanations for the familial occurrence of ovarian cancer in our two patients. First, each sister could have independently acquired a somatic mutation causing carcinoma, especially given that each had risk factors for ovarian

**Table 1**

Genes tested by Ambry 32-gene panel and associated syndromes and cancer risk.

Genetic mutation/syndrome	Genes involved	Organs with increased cancer risk
Mismatch repair defect/Lynch syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Colorectal, uterine, stomach, ovarian, other GI
Hereditary breast/ovarian cancer syndrome	BRCA1, BRCA2	Breast, ovary, pancreas, prostate
Familial adenomatous polyposis	APC	Colon, duodenal, pancreatic, thyroid, other
Ataxia-telangiectasia	ATM	Breast, pancreas
Fanconi anemia-BRCA pathway	BARD1, BRIP1, MRE11A, NBN, RAD50, RAD51C, RAD51D	Breast, ovary
Juvenile polyposis syndrome	BMPR1A, SMAD4	GI tract
MUTYH-associated polyposis	MUTYH	GI tract, colorectal, breast
Proof-reading associated polyposis	POLD1, POLE	Colorectal, adenoma
Pathways associated with increased ovarian cancer risk	CHEK2, PALB2, STK11, TP53	Ovarian, others
PTEN	PTEN	Cowden syndrome (thyroid, uterus, breast), colorectal, renal cell
CDH1	CDH1	Breast, diffuse gastric cancer
Other	CHD1, CDK4, CDKN2A, GREM1, NF1, SMARCA4	Variable

carcinoma including nulliparity secondary to having absent uteri. Neither treating institution completed somatic tumor testing, which would have given a clear answer to this question, and tumor testing is planned upon recurrence to test this hypothesis. A more interesting possibility is that there is an as-yet-unknown genetic mutation not tested for in current gene panels that both sisters carry and predisposed them to developing ovarian cancer. In support of this hypothesis, both sisters developed the same histologic subtype of carcinoma, presented similarly, and responded similarly, although their treatment approaches were different and were carried out at separate institutions. Additionally, the fact that both sisters also have MRKH syndrome, another rare entity with a likely hereditary component, raises the possibility that a single genetic mutation or cluster of mutations inherited by both sisters could connect both disease processes. Importantly, the physiology of MRKH syndrome that results in a lack of communication between the vagina and the Müllerian structures negates the possibility that a transtubal mechanism could explain the connection between MRKH syndrome and ovarian cancer. MRKH syndrome has been associated with Müllerian remnant leiomyomata (Fletcher et al., 2012) and congenital uterine anomalies have rarely been associated with endometrial cancer (Gao et al., 2017). Ovarian cancer has known associations with multiple genetic cancer syndromes including breast-ovarian cancer syndrome, hereditary nonpolyposis colon cancer, Peutz-Jeghers syndrome, PTEN tumor hamartoma syndrome, and MUTYH-associated polyposis (Hereditary, 2008; Lancaster et al., 2015; Mutch et al., 2014). Familial associations involving both endometrial and ovarian cancer (Hereditary, 2008; Lancaster et al., 2015; Mutch et al., 2014; Hemminki and Granström, 2004) point to a physiologic connection between these two organs that could help explain the link between MRKH syndrome and ovarian carcinoma seen in this case report. Alternatively, if the association between MRKH syndrome and ovarian carcinoma in our case report could be elucidated, it may explain developmental and pathologic pathways leading to disease in one or both organ systems.

### 3.1. Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for

review by the Editor-in-Chief of this journal on request.

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