



Case report

Co-occurrence of Mayer-Rokitansky-Küster-Hauser syndrome and ovarian cancer: A case report and review of the literature

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ABSTRACT

Background: Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a congenital disorder of yet unknown etiology, characterized by agenesis/hypoplasia of the müllerian duct system. The occurrence of ovarian cancer (OC) in MRKHS is rare, with < 20 cases reported to date.

Case: A woman affected with MRKHS, developed an abdominal mass at the age of 33 years. Surgical examination revealed a blind vagina, small rudimentary uterus, two fully developed tubes and large bilateral ovarian tumors. The histological diagnosis was a low-grade serous carcinoma (LGSOC) of both ovaries, staged IIB. The patient showed a normal female karyotype and resulted negative at the BRCA1/2 genetic testing.

Conclusion: This is the first report of a LGSOC in a patient with MRKHS. Although the identification of familial cases with both MRKHS and OC raised the hypothesis of a common genetic origin, further data and reports of additional cases are needed in order to assess a possible association of the two conditions.

1. Introduction

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a müllerian duct anomaly characterized by segmental or complete agenesis/hypoplasia of the upper vagina, uterus and, less frequently, fallopian tubes. Its prevalence worldwide is about 1:4500 live female births, representing one of the most frequent congenital malformation affecting the female genital tract and a common cause of primary amenorrhea. Malformations observed in MRKHS may be confined to the müllerian duct (MRKHS type 1 syndrome, Online Mendelian Inheritance in Man reference – OMIM %277000) or involve also other structures, including renal, skeletal, auditory and cardiac (MRKHS type 2 and Müllerian duct aplasia, Renal agenesis/ectopia, Cervical Somite dysplasia -MURCS, OMIM %601076).

The etiological basis of the syndrome is yet to be defined. Most cases are sporadic, though familial clustering has been reported, suggesting a putative genetic origin of the syndrome. However, data on genetic and genomic alterations identified in MRKHS patients, as well as the observed patterns of inheritance, are consistent with a polygenic/multifactorial disorder (Fontana et al., 2017).

In only a few MRKHS cases the occurrence of gynecological cancer was reported. Of particular interest was the report of Huepenbecker et al. describing two sisters affected with MRKHS, who also developed serous ovarian carcinoma (Huepenbecker et al., 2017). This finding

raised the possibility of a shared genetic origin of the two conditions, although data concerning the association of ovarian cancer with MRKHS are still limited.

Herein we report an additional case of serous ovarian carcinoma occurring in a 33-year old woman affected with MRKHS.

2. Case

A 33-year-old Caucasian woman was referred to our Centre for the assessment of an abdominal mass.

Due to primary amenorrhea, at the age of 14 years she underwent gynecological investigations revealing a blind vagina, small rudimentary uterus (3.91 × 1.13 cm), two fully developed tubes and normal ovaries, which led to the diagnosis of MRKH syndrome. No additional malformations were detected at abdominal ultrasound (US) scan and spinal X-ray, with the exception of a slight s-shaped scoliosis. Karyotype analysis resulted normal (46,XX). Her past medical history was unremarkable for other medical conditions.

One month before being referred to our Centre, the patient had experienced abdominal pain and underwent a computed tomography scan revealing the presence of large bilateral ovarian masses with solid and cystic components. Transabdominal and transvaginal US were performed on admission, which showed bilateral adnexal masses with solid components, extending into the pelvis, and monolateral crescent

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Table 1
Cases of Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) patients affected with ovarian tumors.

Article	Country	MRKHS type	Ovarian tumor age at onset	Ovarian tumor histology	Ovarian tumor type	Ovarian tumor grade	Ovarian tumor stage (FIGO)
(Koonings et al., 1991)	United States	I	26	Germ cell	Yolk sac tumor ^a	na	I
(Larsen et al., 1992)	Canada	II	34	Sex-cord stromal	Sertoli cell ^b	II	I
(Pommerehne et al., 1994)	Germany	II	79	Sex-cord stromal	Bilat. Sertoli cell	II	na
(Tsaur et al., 1995)	China	I	4	Germ cell	Immature teratoma	II	I
(Ghirardini and Magnani, 1995)	Italy	I	68	Epithelial	Undifferentiated carcinoma	III	III
(Takeuchi et al., 2006)	Japan	na	8	Germ cell	Yolk sac tumor	na	I
(Mishina et al., 2007)	Moldova	na	35	Germ cell	Dysgerminoma	na	I
(Kavallaris et al., 2011)	Germany	II	48	Epithelial	Mixed epithelial carcinoma	III	III
(Bae et al., 2013)	Korea	II	31	Epithelial	Serous papillary ^c	na	III
(Ko et al., 2012)	Korea	II	37	Epithelial	Serous carcinoma	III	III
(Nusrath et al., 2016)	India	II	65	Epithelial	Endometrioid carcinoma	na	I
(Juusela et al., 2017)	United States	I	72	Sex-cord stromal	Bilat. Sex-cord stromal tumor	na	I
(Huepenbecker et al., 2017)	United States	na	64	Epithelial	Serous carcinoma	III	III
		na	63	Epithelial	Serous tubal carcinoma	III	III
Present Case	Italy	I	33	Epithelial	Bilat. Serous carcinoma	I	II

na, not available.

^a Previous diagnosis of femur osteosarcoma at the age of 25, no chemotherapy or radiation therapy.

^b Borderline tumor of the other ovary.

^c Supernumerary ovary.

sign. Right adnexal mass measured 65 × 58 × 74 mm, left mass measured 35 × 37 × 34 mm. A small uterus with no endometrial cavity was identified. A diagnosis of borderline ovarian tumor vs. carcinoma was suspected and a surgical approach was discussed with the patient.

Preoperative CA-125 level was elevated (3488 U/ml), other tumor markers (CEA, AFP, CA15.3, CA19.9) were in the normal range. Radical surgery with bilateral salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy was performed. Surgical findings included multiple omental and peritoneal nodules, adnexal masses (max diameter: right 70 mm, left 40 mm) with papillary vegetations and uterine aplasia. Samples from peritoneal washing and multiple peritoneal biopsies were obtained. Hystopathological examination evidenced a low-grade serous carcinoma at both the ovaries, which was also localized at the anterior wall of the rectum; fallopian tubes showed no neoplastic invasion. Findings of the omental and peritoneal nodules included psammoma bodies and no evidence of cancer cells. No signs of residual disease were detected and the tumor was staged IIB (FIGO). Postoperative recovery was unremarkable. The patient received six cycles of adjuvant chemotherapy with carboplatin.

Due to the personal history of early onset ovarian carcinoma, the patient was referred to genetic counseling. At pedigree evaluation, the patient reported a post-menopausal breast cancer in her paternal grandmother, Hodgkin disease in the paternal grandfather and colon cancer in a maternal uncle. Although her cancer family history was not suggestive of a specific cancer predisposition syndrome, *BRCA1* and *BRCA2* analysis was discussed and performed by means of Next Generation sequencing and multiplex ligation-dependent probe amplification (MLPA), which resulted negative for either germline pathogenic variants or variants of uncertain significance.

3. Discussion

Ovarian cancer (OC) is a common gynecological disease with > 230'000 new cases per year worldwide, accounting for about 3,5% of all newly diagnosed cancers. The estimated lifetime risk of developing OC is 1,3%, although incidence varies widely depending on both age and histological type.

> 90% of ovarian malignancies are of epithelial origin, which include five main histological subtypes: high-grade serous (HGSOC, ~70%), endometrioid (~10%), clear cell (~10%), mucinous (~3%) and low-grade serous (LGSOC, < 5%). Non-epithelial histologies, which

account for about 10% of OCs, include sex-cord stromal tumor (~5%) and germ cell tumor (~2%). For all epithelial subtypes, incidence rates before ages 35–39 are very low. However, the incidence steadily increases with age, reaching the highest rate at 70–80 years. Notably, at ages younger than 30 years the incidence of other histotypes is higher than that of epithelial OC (Coburn et al., 2017).

According to these data, albeit OC is not a rare disease, our patient affected with LGSOC at the age of 33 years developed an infrequent tumor at an uncommon age. Due to the atypical presentation, a possible genetic predisposition was considered.

The main susceptibility genes associated with an increased risk of OC are *BRCA1* and *BRCA2*, although pathogenic variants in these genes usually underlie the development of HGSOC but not LGSOC. Despite the tumor histotype, due to the very early age at onset, genetic testing of the *BRCA1/2* genes was offered to the patient. The analysis resulted negative for germline variants, confirming the hypothesis of a different pathomechanism for LGSOC. Other genetic analyses were not considered because the patient's family history was not suggestive for any specific cancer predisposition syndrome (eg. Lynch syndrome).

In patients with MRKHS, OC is only occasionally described. To the best of our knowledge, only 14 cases have been reported worldwide: four from Europe, five from Asia and five from America. Information concerning patients affected with both MRKHS and OC are summarized in Table 1. Among all MRKHS patients with OC, eight (53%) developed an epithelial cancer, most of the serous type (5/8), four (27%) developed a germ cell tumor and three (20%) a sex-cord stromal tumor. None of the previously reported patient developed a LGSOC. Median age at onset was 55 years (range 31–68) for epithelial tumors, 30 years (range 4–79) for non-epithelial tumors. Although the limited number of cases is not suitable for a statistical analysis, epithelial cancers appear to occur at a younger age in MRKHS patients compared with the general population. Of note, two additional patients from Korea were diagnosed before age 40 years. However, the OC described by Bae and colleagues (Bae et al., 2013), arose from a supernumerary pelvic ovary, which could be at higher risk for tumor development.

Genetic testing in other cases was not performed, with the exception of the two sisters reported by Huepenbecker, who were affected with MRKHS and developed HGSOC at the age of 63 and 64 years respectively. Both these patients resulted negative for pathogenic variants in *BRCA1/2* and other 31 cancer susceptibility genes (Huepenbecker et al., 2017). Moreover, no data on cancer family history are available for

previously reported patients, therefore it is not possible to rule out that a putative cancer-predisposing syndrome might explain a subset of these cases.

4. Conclusions

In conclusion, we report on a new case of co-occurrence of MRKHS and OC and provide an updated review of the literature. To date, there is no evidence of an involvement of known cancer genes in MRKHS, as opposed to other genitourinary malformation syndromes, such as Denys-Drash syndrome (OMIM #194080) or WAGR (OMIM #194072), both characterized by a loss of function of the WT1 gene. Since the available data and knowledge about the etiopathological factors underlying the syndrome are still limited, it is not possible to define a putative correlation between MRKHS and increased risk for OC. The collection of further data and reports of additional cases will thus be crucial in order to either confirm or rule out a possible common pathomechanism underpinning MRKHS and OC.

4.1. 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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Author contribution

R.V. and J.A. revised the data and drafted the manuscript; B.P. and S.M. collected the clinical and genetic data and S.M. revised the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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