

Case report

Uterine cervical cancer associated with obstructed hemivagina and ipsilateral renal agenesis (OHVIRA) syndrome: A case report and review of the literature

Emiko Oka¹, Tatsuyuki Chiyoda^{*}, Takashi Iwata, Wataru Yamagami, Daisuke Aoki

Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan

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1. Introduction

Obstructed hemivagina and ipsilateral renal agenesis (OHVIRA) syndrome (Herlyn-Werner-Wunderlich syndrome) is one of the rare congenital Müllerian duct anomalies, which presents with a uterus didelphys, renal anomalies, and a hemivagina. This syndrome results from a lateral fusion defect of the Müllerian ducts with asymmetric vaginal obstruction (Kaba et al., 2013). Cervical cancer associated with these malformations is a very rare occurrence. We herein report a case of uterine cervical cancer associated with OHVIRA syndrome; the preoperative evaluation of tumor spread was difficult.

2. Case report

The patient was a 38-year old female, gravida 0, para 0. She underwent marsupialization for hematocolpos of the left side of vagina at the age of 22. Then, uterus didelphys and left renal agenesis were identified, and she was diagnosed with OHVIRA syndrome.

She presented at the hospital with intermenstrual bleeding, and was then transferred to our institution with a suspicion of cervical cancer. Initial pelvic examination revealed no abnormality in the visible part of her uterine cervix, however macroscopic tumor was observed at the left vaginal septum (Fig. 1A and B). The result of cervical and vaginal cytology was adenocarcinoma, and biopsy of the tumor at the vaginal wall confirmed the tumor as adenocarcinoma. We performed human papillomavirus (HPV) typing using the PYGY line blot assay which is a

reliable HPV genotyping method (Kondo et al., 2012) the result of which was negative. The left cervix was not visible by colposcopy. A pelvic magnetic resonance imaging revealed a 16 mm cervical mass arising from the left cervix, with left anterior vagina wall infiltration (Fig. 1C). There was no tumor involvement of the lower third of the vagina, and no parametrial invasion. Computed tomography showed neither metastasis nor lymphadenopathy. Positron emission tomography also showed no metastasis. The diagnosis of the International Federation of Gynecology and Obstetrics (FIGO) stage II A1 cervical cancer was confirmed.

The patient underwent abdominal radical hysterectomy. Intraoperative findings found that the uterus consisted of two distinct uterine bodies and cervixes. A 26 × 25 mm left cervical mass was identified (Fig. 2A). Cancer macroscopically had infiltrated into the vaginal wall, thus the vaginal wall was additionally excised for 1 cm. The surgical margin of the vagina was 24 mm from the macroscopic tumor. There were no apparent tumors in the right side of the uterus and in either fallopian tube. No left ureter was found, as preoperative examinations had suggested. There were three branches from the left internal iliac vein to the left hypogastric fascia, and branches of the left internal iliac vein were more complex than those on the right.

Postoperative histopathology confirmed endocervical adenocarcinoma, usual type with invasion into the vaginal wall (Fig. 2B). Immunohistochemistry showed the tumor was positive for p16^{INK4a} (Fig. 2C). HPV typing by the PYGY line blot assay using macro-dissected formalin-fixed paraffin-embedded (FFPE) specimens again confirmed that the tumor was negative for HPV. The depth of invasion was 7 mm. The

^{*} Corresponding author at: Department of Obstetrics and Gynecology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail address: chiyoda@keio.jp (T. Chiyoda).

¹ Present address: Department of Obstetrics and Gynecology, Osaka University School of Medicine, Osaka, Japan.

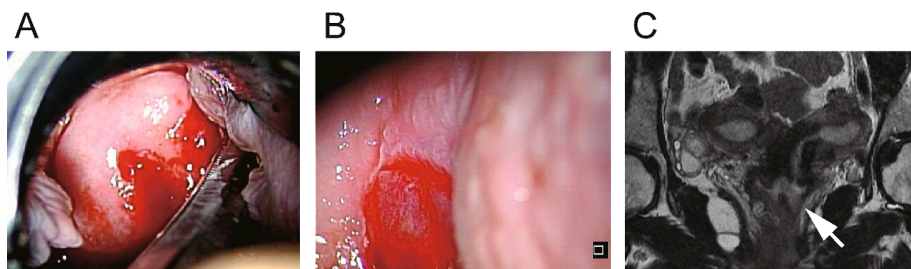


Fig. 1. Colposcopy demonstrated the cervix with no gross tumor (A). Tumor was identified in the left side of the vaginal wall (B). T2-weighted magnetic resonance imaging (coronal section). Uterine cervical tumor was detected on the left side of the uterine cervix to vaginal wall (Arrow) (C).

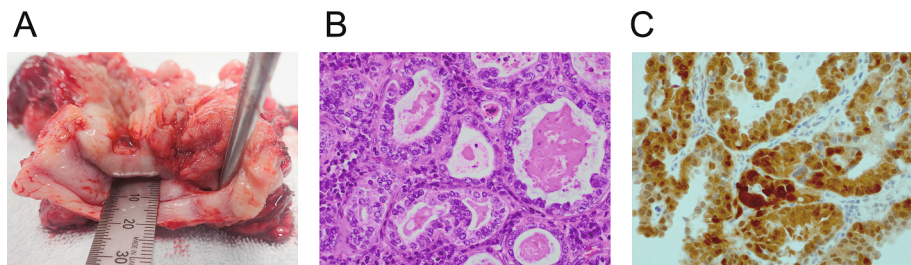


Fig. 2. Surgically resected tissues. Cervical adenocarcinoma was detected on the left side of the uterine cervix (A). Histopathological findings of the hysterectomy sample showed endocervical adenocarcinoma, usual type (hematoxylin-eosin stain, $\times 40$) (B). The tumor was positive for p16^{INK4a} (C).

vaginal surgical margin was positive for adenocarcinoma. Lymphovascular space invasion was also positive. Parametrial tissue was free of tumor. There was no lymphatic metastasis of the adenocarcinoma.

The patient's postoperative course was uneventful. Following the surgery, she underwent concurrent chemoradiotherapy using volumetric modulated arc therapy at a dose of 50.4 Gy in 28 fractions for whole pelvis followed by intracavity brachytherapy at a dose of 10 Gy in two fractions. Two years later, the patient is being followed up without any treatment-related complications or signs of recurrence.

3. Discussion

OHVIRA syndrome is characterized by uterus didelphys, an obstructed hemivagina and ipsilateral renal anomaly. It is a Müllerian duct anomaly, due to abnormal embryologic development of the urogenital system (Fedele et al., 2013). The fallopian tubes, uterus and upper two-thirds of the vagina are derived from Müllerian ducts. Their appropriate development requires fusion and resorption of the separating wall between both right and left Müllerian ducts. It is induced by the Wolffian ducts, which arise as the urinary system. Therefore, female genital tract malformations caused by congenital Müllerian duct anomalies are often associated with urinary tract malformations.

Cervical cancer in uterus didelphys is an extremely rare occurrence, and there have been very few reports. We found four case reports, including five patients with OHVIRA syndrome associated with cervical cancer (Cordoba et al., 2017; Kaba et al., 2013; Kusunoki et al., 2018; Watanabe et al., 2012). We compared several points in six cases, including ours (Table 1). Age at surgical treatment ranged from 33 to 65 years, with a median age of 43.5 years. Chief complaints included genital bleeding in all cases. Interestingly, all cases of cervical cancer associated with OHVIRA syndrome occurred on the nonvisible side of cervix. Our case was HPV negative, using both cytology and FFPE samples, although p16^{INK4a} staining was positive. p16^{INK4a} staining was reported as positive in 25% of HPV-negative cervical cancer patients (Rodríguez-Carunchio et al., 2015). HPV-negativity is recognized as occurring more frequently in adenocarcinomas than in squamous cell carcinomas. It has been reported that approximately 30% of classic mucinous adenocarcinoma (usual endocervical type, villoglandular type, and intestinal type) are HPV negative, and nonmucinous

adenocarcinoma (clear cell, serous, minimal deviation, and endometrioid) are more frequently HPV negative (70–90%) (Pirog et al., 2014). Among the six cases reported including ours, HPV information was available in three cases, all of which were negative (Table 1). Of note, no patient was diagnosed as having squamous cell carcinoma. Histologic subtypes of six adenocarcinomas are as follows; four cases of non-mucinous adenocarcinoma (endometrioid: 2, clear cell: 2), one case of endocervical adenocarcinoma, usual type, and one case of adenocarcinoma without detailed information (Table 1). This indicates that in OHVIRA syndrome, non-HPV related adenocarcinoma can occur on the nonvisible side of cervix. There are two hypotheses regarding the association between adenocarcinoma and Müllerian duct anomalies. One hypothesis is that the tumor may have arisen from the paracervix of Müllerian-derived columnar epithelium subjected to genetic and hormonal changes for an extended period of time (Kusunoki et al., 2018). The second hypothesis is that it arises from endometriosis. The non-visible side of the cervix is exposed to menstrual blood for an extended time. Then, transportation of basal endometrium fragments into cervix may occur. Malignant transformation of endometriosis may be present in women with OHVIRA syndrome (Peiretti et al., 2008). More reports of OHVIRA syndrome patients associated with cervical cancer are necessary in order to elucidate the mechanisms of carcinogenesis. It may be possible that HPV-related cervical cancer on the visible side of cervix associated with OHVIRA syndrome has just not been reported.

There are two varieties of hemivagina; i.e. obstructed and semi-obstructed. In those who have not undergone surgical treatment for hemivagina, it is very difficult to find both cervixes on colposcopy. In addition, postoperative vaginal stenosis can occur (Smith and Laufer, 2007). It reported that it is also difficult to find both cervixes in colposcopy, even in those who undergone a surgical procedure such as vaginoplasty. Examination of the nonvisible side of the vagina and uterus is necessary for the OHVIRA syndrome patients with metrorrhagia, even when the visible side demonstrates no abnormal findings.

In conclusion, we experienced a case of cervical cancer occurring on the nonvisible side of cervix with OHVIRA syndrome diagnostic evaluation of the tumor was difficult. Combining colposcopy-directed biopsy and medical imaging are important for women with OHVIRA syndrome who have metrorrhagia or menorrhagia. The clinician should be aware that in Müllerian anomalies, cervical malignancies may be overlooked,

Table 1
Cervical cancer case reports of OHVIRA syndrome.

	Age (yr)	Gravida/Para	HPV	Visual uterine cervix	Diseased uterine cervix	Cytologic result	Preoperative histologic result	Stage	Operation for hemivagina	Chief complaint	Postoperative histologic result
Kusunoki et al. 2018	65	gravida 3, para 2	Unknown	Left	Right	NILM	Normal (left cervix)	pT1b2N0M0	No information	Metrorrhagia	Clear cell adenocarcinoma
Cordoba et al. 2017	37	gravida 2, para 2	Unknown	Right	Left	Unknown	Adenocarcinoma	IIIA	Yes	Menorrhagia, metrorrhagia	Adenocarcinoma
Kaba et al. 2013	49	gravida 2, para 2	Unknown	Right	Left	NILM	Endometrioid adenocarcinoma (endometrium)	IB1	No information	Menorrhagia, metrorrhagia	Endometrioid type cervical adenocarcinoma
Watanabe et al. 2012	33	gravida 2, para 2	Negative	Left	Right	NILM	Endometrioid adenocarcinoma (vaginal septum)	IVA	No information	Metrorrhagia	Endometrioid adenocarcinoma
	53	gravida 2, para 2	Negative	Left	Right	NILM	Adenocarcinoma cells (aspiration smear from vaginal fistula)	I	Yes	Vaginal pain, metrorrhagia	Clear cell adenocarcinoma
Our case	38	gravida 0, para 0	Negative	Right	Left	Adenocarcinoma	Adenocarcinoma (vaginal septum)	IIA1	Yes	Metrorrhagia	Endocervical adenocarcinoma, usual type

causing delays in tumor diagnosis.

4. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written informed consent is available for review by the Editor-in-Chief of this journal on request.

Author Contributions

E.O. assisted with surgery, acquired the clinical data and wrote the manuscript; T.C. assisted with surgery, acquired the clinical data and wrote the manuscript; T.I. contributed to HPV testing; W.Y. contributed to discussion; D.A. performed surgery and edited 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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Department of Obstetrics and Gynecology, Keio University School of Medicine.

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