Case report

Herlyn-Werner-Wunderlich syndrome (HWWS)-associated gynecological malignancies: A case report and literature review

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ABSTRACT

Herlyn-Werner-Wunderlich syndrome (HWWS) is a rare congenital urogenital anomaly characterized by uterine didelphys, unilateral blind hemivagina, and ipsilateral renal agenesis. We present a very rare case of HWWS-associated cervical cancer in which the presence of a genital anomaly was not noticed until the patient experienced postmenopausal vaginal bleeding. A 74-year-old nulliparous Japanese woman presented with vaginal bleeding. Pre-treatment workup revealed uterine didelphys, obstructed hemivagina/hemicervix, renal agenesis, and cancer development from the remnant-obstructed hemivagina/hemicervix. The patient was diagnosed with HWWS and HWWS-associated vaginal or cervical cancer, treated with radical surgery, and a diagnosis of clear cell carcinoma (CCC) of the uterine cervix was histopathologically confirmed. A literature review revealed an increased incidence of CCC in women with HWWS.

1. Introduction

Herlyn-Werner-Wunderlich syndrome (HWWS), also known as OHVIRA (Obstructed Hemivagina and Ipsilateral Renal Anomaly) syndrome, is a rare congenital abnormality caused by abnormal development of Müllerian and Wolffian ducts (Burgis, 2001). HWWS was originally characterized by three key anomalies: uterus didelphys, unilateral blind hemivagina, and ipsilateral renal agenesis, and its incidence is estimated to be 0.1–3.8% (Burgis, 2001).

HWWS is commonly diagnosed during puberty and presents with pelvic pain or dysmenorrhea shortly after menarche, all of which are associated with hematocolpos, hematometra, or hematosalpinx (Zhu et al., 2015). However, in asymptomatic cases during puberty and the subsequent period, the diagnosis of HWWS is delayed, and unusual presentations of HWWS, including renal or vaginal hemorrhage, endometriosis, infertility, and benign and malignant tumors of the genitourinary system, have been observed (Jindal et al., 2009). With regard to HWWS-associated malignant gynecological cancer, only 11 cases, including ours, have been reported in the English literature (Watanabe et al., 2012; Kaba et al., 2013; Cordoba et al., 2017; Kusunoki et al., 2018; Oka et al., 2020; Mei, 2020; Tanase et al., 2021; AlMulhim and AlRasheed, 2021; Kobayashi et al., 2021). Given the rarity of this condition, we believe that reporting individual cases is important for establishing an optimal diagnostic method and treatment.

We present a very rare case of HWWS-associated cervical cancer in which the presence of a congenital genital anomaly was not noticed until the patient experienced postmenopausal vaginal bleeding and was successfully treated with radical hysterectomy plus total vaginectomy. We also summarized the current knowledge regarding HWWS-associated gynecological cancers.

1.1. Informed consent statement

A written informed consent was obtained from the patient for publication of this case report and accompanying images.

1.2. Case report

A 74-year-old nulliparous Japanese woman who had been evaluated at a general hospital for postmenopausal vaginal bleeding was referred to our hospital. Her surgical and medical history was unremarkable, except for hypertension. After her menarche at age 15, she had regular cycles without dysmenorrhea and experienced menopause at 50. She was informed about her left kidney agenesis during childhood.

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On speculum evaluation, a macroscopic tumor sized 1-cm was observed at the left vaginal wall, 2-cm above the vaginal opening. A biopsy obtained from this lesion revealed adenocarcinoma. She had a grossly normal but slightly right-shifted uterine cervix with a normal pap smear result. Transvaginal ultrasound revealed a 4-cm cystic mass adjacent to her normal cervix, which was later proven to be a hydro- 
metra without accompanying abnormal endometrial thickness on pelvic MRI (Fig. 1A).

Bimanual pelvic examination revealed a 5–6 cm immovable mass on the left anterior side of the abovementioned 4-cm cystic mass that extended to the left vaginal lesion. Transvaginal ultrasonography revealed that the mass consisted of two parts: a 2-cm round solid mass adjacent to the left vaginal tumor (lower solid portion), which communicated with a 3–4 cm cystic mass with internal echoes resembling an endometrioma (superior cystic portion). Based on pelvic MRI (Fig. 1B), the solid and cystic structures were thought to correspond to a malignant tumor that developed from a left obstructed hemivagina/ 
hemicervix and a resulting hematometra, respectively. In addition, on the left side of the obstructed hemivagina/hemicervix, another fluid-filled tubular structure exhibiting high signal intensity on T1-weighted image was observed (Fig. 1C), which corresponded to a blind ectopic ureter containing the reflux of hematic fluid from the obstructed hemivagina/hemicervix. Both the ovaries were normal.

Given the presence of left renal agenesis (Fig. 1D), uterine didelphys (two separate hematomas), and an obstructed hemivagina/hemi 
cervix, a diagnosis of Herlyn-Werner-Wunderlich syndrome (HWWS) and a provisional diagnosis of adenocarcinoma extending from the obstructed hemivagina/hemicervix were made. Computed tomography (CT) scans of the abdomen and chest showed no evidence of metastatic disease, and laboratory findings were unremarkable, except for an elevated serum CA-125 of 69.3 U/mL (normal range < 35 U/mL).

After discussing the treatment options, including surgical treatment and definitive radiotherapy, with the patients and their families, the patient received surgical treatment. During surgery, no intraoperative adhesions, uterine didelphys and normal adnexa on either side were noted. Radical hysterectomy, total vaginectomy, bilateral salpingo 
ophorectomy, and pelvic lymphadenectomy were performed to resect the tumor with adequate surgical margins. During the procedure, a fluid-filled tubular structure was identified on the left side of her obstructed hemivagina/hemicervix, which was proven to be her left ectopic ureter leading to the obstructed hemivagina/hemicervix and was resected along with her obstructed hemivagina/hemicervix.

Pathological examination of the surgical specimen revealed a clear cell carcinoma that developed from the obstructed hemivagina or hemicervix extending superficially to the uterine corpus without lymph node metastasis (Fig. 2). Pathological examinations failed to distinguish the origin of the adenocarcinoma (vagina vs. cervix). The surgical margin was negative, and parametrial or lymphovascular space invasion was not observed. Although a vaginal tumor was predominant, as the uterine cervix was involved, we concluded that this was a cervical cancer of the remnant uterus (T2A1N0M0). Due to the lack of clinical evidence demonstrating the benefit of adjuvant radiotherapy for such unusual cervical cancer that developed from the remnant uterus, the patient did not receive postoperative adjuvant treatment. She is currently free of disease three months after the radical surgery.

2. Discussion

We present a very rare case of HWWS-associated cervical cancer, in which the presence of a congenital genital anomaly was not noticed until the patient experienced postmenopausal vaginal bleeding. After the diagnosis of HWWS and vaginal or cervical cancer extending from the non-visible obstructed hemivagina/hemicervix, the patient was successfully treated with radical hysterectomy, total vaginectomy, and pelvic lymphadenectomy. Postoperative histopathology revealed a clear cell carcinoma that developed from the obstructed hemivagina/
uterus and simple vagina in the presence of an isolated hemicervix and described an association between right renal aplasia and a bicornuate uterus (Herlyn and Werner, 1971). Five years later, in 1976, Wunderlich described adenocarcinoma, VB; vaginal bleeding.

chemoradiotherapy, LND; lymphadenectomy, EBRT; external-beam radiotherapy, PE; pelvic exenteration, CCC; clear cell carcinoma, EM; endometrioid carcinoma, A; adenocarcinoma, VB; vaginal bleeding.

Table 1

| Author Reference | Year | Age | Gravida/Para | HPV status | DES status | Affected side | Pretreatment diagnosis | Treatment | Posttreatment diagnosis | Histology | Previous diagnosis of HWWS | Symptom |
|------------------|------|-----|-------------|------------|------------|---------------|------------------------|-----------|-------------------------|-----------|--------------------------|---------|
| Watanabe, et al. 1 | 2012 | 33 y.o. | 2/2 | Negative | No | Remnant | Cervical or vaginal cancer | Chemotherapy, EBRT, followed by PE RH | Cervical or vaginal cancer | EM | Yes | VB |
|  |  | 53 y.o. | 2/2 | Negative | No | Remnant | Cervical or vaginal cancer | Chemotherapy, EBRT, followed by PE RH | Cervical or vaginal cancer | EM | Yes | VB |
| Kaba, et al. 5 | 2013 | 49 y.o. | 2/2 | NA | NA | Remnant | Corpus cancer | Radical surgery | Cervical cancer | EM | No | Dysmenorrhea |
| Cordoba, et al. 8 | 2017 | 37 y.o. | 2/2 | NA | NA | Remnant | Cervical cancer | Pelvic LND followed by CCRT | Cervical cancer | T1N1M0 | A | Dysmenorrhea |
| Kusunoki, et al. 9 | 2018 | 65 y.o. | 3/2 | NA | No | Remnant | Paracervical mass in the remnant uterus | Radical surgery followed by CCRT | Cervical cancer | T1R2N0M0 | A | Dysmenorrhea |
| Oka, et al. 9 | 2020 | 38 | 0/0 | Negative | No | Remnant | Cervical cancer | Radical surgery followed by RT | Cervical cancer | T2A1N0M0 | A | Dysmenorrhea |
| Mei, et al. 9 | 2020 | 40 | NA | No | Remnant | Vaginal cancer | Radical surgery | Vaginal cancer | T1N0M0 | CCC | VB |
| Tanase, et al. 10 | 2021 | 1/1 | NA | No | Remnant | Cervical cancer | Radical surgery | Vaginal cancer | T1N0M0 | CCC | VB |
| Almulhim, et al. 11 | 2021 | 52 y.o. | 0/0 | NA | NA | Right ovary | Ovarian tumor | Cystectomy | Ovarian cancer | T1AnM0 | Serous borderline tumor | VB |
| Kobayashi, et al. 12 | 2021 | 29 y.o. | 0/0 | NA | NA | Visible side uterus | Uterine corpus | Radical surgery | Corpus cancer | T3A1N0M0 | EM | VB |
| Current case | 74 y.o. | 0/0 | NA | No | Remnant | Cervical or vaginal cancer | Radical surgery | Cervical cancer | T2A1N0M0 | CCC | VB |

NA; not available, HPV; Human papillomavirus, DES; diethylstilbestol, HWWS; Herlyn-Werner-Wunderlich syndrome, RH; radical hysterectomy, CCRT; concurrent chemoradiotherapy, LND; lymphadenectomy, EBRT; external-beam radiotherapy, PE; pelvic exenteration, CCC; clear cell carcinoma, EM; endometrioid carcinoma, A; adenocarcinoma, VB; vaginal bleeding.
As shown (Table 1), so far, 11 cases of HWWS-associated gynecological malignancies have been reported. Most malignancies developed from the remnant uterus or vagina (nine cases), and vaginal bleeding was the most frequent presenting symptom. Of these, six patients had been previously diagnosed with HWWS. Of the five patients who had received marsupialization for HWWS, four patients had a correct pre-treatment diagnosis of gynecological cancer, which was completely consistent with a postoperative diagnosis. In contrast, among the 5 patients who had not been previously diagnosed with HWWS, a preoperative diagnosis of gynecological cancer was not consistent with a postoperative diagnosis in 3 cases, indicating the difficulty in precisely diagnosing cancer developed from the remnant uterus or vagina in women with HWWS.

To the best of our knowledge, this is the third case of HWWS-associated CCC of the uterine cervix. Among the reported HWWS-associated gynecological cancers, clear CCC was predominant, followed by endometrioid carcinoma (Table 1). It has been generally accepted that CCC of the vagina or cervix is extremely rare, except for women with a history of prenatal diethylstilbestrol (DES) exposure. No such DES-associated cases were observed in the HWWS-associated gynecological cancers (Table 1). Interestingly, the histological trend in which CCC and endometrioid carcinoma are predominant is consistent with that observed in endometriosis-associated ovarian cancer (Murakami et al., 2020 Jun 24). The precise reason for this trend is unknown, but human papillomavirus (HPV) cannot, as cervical or vaginal CCC is known to be an HPV-independent tumor (Stolnicu et al., 2022). We believe this can be explained by a common feature between obstructed hemivagina/hemicervix in HWWS and ovarian endometriosis: accumulation of menstrual blood containing excess iron and iron-induced reactive oxygen species, which theoretically can accelerate malignant transformation of exposed cells by inducing gene mutations or DNA methylation (Stolnicu et al., 2022). However, as there is no evidence to support this hypothesis, future mechanistic investigations using clinical samples obtained from the affected patients are warranted.

In summary, we presented a case of HWWS-associated cervical cancer in which postmenopausal vaginal bleeding was the first presentation of HWWS and cancer development from the remnant vagina. Given the rarity of the condition, sharing this knowledge may not impact daily patient care. However, we believe that it is worth remembering that HWWS may be present in the elderly, even without a previous diagnosis of urogenital anomaly or history of dysmenorrhea or abdominal/pelvic pain. Moreover, although cancer development in the remnant gynecological organs is extremely rare and a diagnosis is challenging, to avoid a delay in early diagnosis, this condition should be considered when women suspected of having HWWS exhibit postmenopausal vaginal bleeding.

Ethical approval status: The Ethics Committee of Osaka International Cancer Institute decided that this case report does not require IRB approval due to the nature of the study: a report describing the diagnosis and the treatment of a single patient and thus does not meet the definition of human subjects research.