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Uterus didelphys and cervical cancer: A case report

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ABSTRACT

Background: Deficiencies in the merging process of the paramesonephric ducts as part of the embryonal development lead to anomalies of the uterus, cervix, fallopian tubes and proximal vagina (Müllerian malformations). The co-occurrence with cervical cancer is rare and there are no standardized protocols for managing urogenital anomalies in the realm of oncologic treatment for gynecological carcinomas.

Case report: A symptom-free 41-year-old woman (gravida 0) presented at our clinic with an externally obtained AGC-FN (atypical glandular cells – favor neoplastic) finding in the Papanicolaou (Pap) smear test and persistent positivity for human papillomavirus (HPV) type 16. Sample biopsies from the portio vaginalis uteri confirmed a cervical intraepithelial neoplasia (CIN) III/ high grade squamous intraepithelial lesion (HSIL), invasive carcinoma could not be ruled out. The examinations revealed the incidental finding of a uterus didelphys and renal agenesis on the left side. After cervical conization, the patient was diagnosed with squamous cell carcinoma of the cervix. Guideline-compliant treatment with laparotomic hysterectomy according to Piver type II following a staging laparoscopy with sentinel lymphadenectomy was performed. A customized protocol was used for the indocyanine green (ICG) injection as part of the sentinel lymph node examination, tailored to the patient's anatomical characteristics.

Discussion: Müllerian malformations may impede detection and treatment of gynecological carcinomas. Individualized therapy planning is necessary to meet the anatomical peculiarities of the genital anomaly. In instances of concomitant urinary tract anomalies, protective measures are imperative to safeguard normal kidney function.

Conclusion: The current case demonstrates the successful implementation of guideline-compliant therapy for early-stage cervical cancer in an individual with Müllerian malformation.

1. Background

Deficiencies in the merging process of the paramesonephric ducts (Müllerian ducts) as part of the embryogenesis lead to anomalies of the uterus, cervix, fallopian tubes and proximal vagina (e Passos and Britto, 2020; Kiblboeck et al., 2023). Müllerian malformations comprise a wide range of subtypes and in cases of additionally impaired mesonephric duct (Wolffian duct) development, they are associated with renal or urinary tract anomalies (e Passos and Britto, 2020; Kiblboeck et al., 2023; Cordoba et al., 2017). Possible symptoms include primary amenorrhea, dysmenorrhea, sexual dysfunction, pelvic pain and limited fertility (e Passos and Britto, 2020). However, Müllerian malformations can also remain clinically silent (e Passos and Britto, 2020; Kiblboeck et al., 2023). This factor adds to the complexity of accurately estimating the incidence of female genital malformations. The reported incidences vary widely, ranging from 0.2 to 6.7 % (Kiblboeck et al., 2023). Although cervical carcinoma is one of the most common types of cancer in women worldwide, the co-occurrence with cervical cancer is rare and to date, almost exclusively case reports are available in the literature (Cordoba et al., 2017; Matylevich et al., 2022; Mabuchi et al., 2022; Lei et al., 2021; Lei et al., 2020; Zong et al., 2019; Kusunoki et al., 2018; Kaneyasu et al., 2019; Sung et al., 2021). Urogenital anomalies can

Abbreviations: AGC-FN, atypical glandular cells – favor neoplastic; CIN, cervical intraepithelial neoplasia; CT, computed tomography; G0, nulligravidous; HPV, human papillomavirus; HSIL, high grade squamous intraepithelial lesion; HWWS, Herlyn-Werner-Wunderlich syndrome; ICG, indocyanine green; LSIL, low grade squamous intraepithelial lesion; MRI, magnetic resonance imaging; OHVIRA, obstructed hemivagina and ipsilateral renal anomaly; Pap, Papanicolaou; TNM, tumor, node, metastases.

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complicate oncological treatment of gynecological carcinomas (Matylevich et al., 2022; Lei et al., 2021; Zong et al., 2019). By presenting the following case, our aim is to contribute towards enhancing the diagnostics and treatment of patients with both, Müllerian malformation and cervical cancer.

2. Case report

A 41-year-old nulligravidous woman presented at our clinic with an externally obtained abnormal cytological finding in the Papanicolaou (Pap) smear test, PAP III-g (according to Munich Nomenclature III)/ atypical glandular cells – favor neoplastic (AGC-FN; according to the Bethesda System 2014), without clinical symptoms. A positivity for human papillomavirus (HPV) type 16 had already been known since the year of 2020. Otherwise, the medical history revealed no relevant previous diseases. Apart from an oral contraceptive, the patient did not take medication on a regular basis. The patient documented the onset of menarche at the age of 16. Prior to commencing oral contraceptive use, menstrual bleeding followed a regular pattern, albeit accompanied by recurrent episodes of dysmenorrhea. Both regular menstruation and perimenstrual discomfort ceased upon initiation of hormonal contraception. The patient's family planning had been finalized by the time of her consultation. Risk factors such as promiscuity or nicotine abuse were negated by the patient.

The colposcopy showed a partly polypous altered portio vaginalis uteri with a highly vulnerable ectopia (Fig. 1). After application of acetic acid solution, a diffuse delicate white coloration appeared in the ectopic area. Overall, the colposcopic findings were suspicious for invasive carcinoma. There was no indication of a second portio vaginalis uteri in the clinical examination with the speculum. However, the transvaginal ultrasound revealed a uterus didelphys with two cervices (Fig. 2). Sample biopsies from the portio vaginalis uteri confirmed a cervical intraepithelial neoplasia (CIN) III/ high grade squamous intraepithelial lesion (HSIL), invasive carcinoma could not be ruled out. Conization of the cervix uteri with subsequent cervical curettage was indicated. Intraoperatively after conization, two separate cervical canals were found with a common outlet into one portio vaginalis uteri. The histological findings of the cone biopsy indicated a moderately differentiated, p16-positive, non-keratinizing basaloid squamous cell carcinoma of the cervix, associated with extensive HSIL. The cervical carcinoma as well as the HSIL were excised completely with clear margins, TNM (tumor, node, metastases) stage pT1b1 L0 V0 Pn0 G2 R0 Ris0. The histopathological processing of the curettage material revealed dysplasia-free endocervical mucosa. Further imaging was indicated. During staging examinations, which included magnetic resonance imaging (MRI) of the pelvis and full body computed tomography (CT), renal agenesis was detected on the left side (Fig. 3). The full clinical presentation of Herlyn-Werner-Wunderlich syndrome (HWWS), which is characterized not only by uterus didelphys and unilateral renal agenesis, but also by ipsilateral blind hemivagina (Mabuchi et al., 2022), did not manifest in our patient.

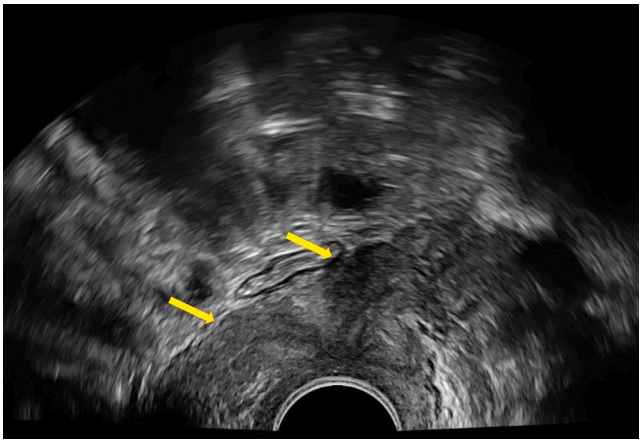

Fig. 2. Sonographic evidence of two cervices.

In accordance with the current guidelines, the patient underwent staging laparoscopy with pelvic sentinel lymphadenectomy. The intraoperative findings confirmed a uterus bicornis completus (Fig. 4). Both uterine horns were attached to the pelvic wall and thus immobile. The ovaries and fallopian tubes showed no abnormalities. The upper abdominal organs (liver, gallbladder and stomach) appeared unremarkable. On the right side, there was a normal ureter whereas on the left side, no ureter could be identified. For the purpose of sentinel lymph node mapping, indocyanine green (ICG) was injected into the cervical stroma of both cervices. The ICG-injection was administered at the 5, 7, and 12 o'clock positions. The patient's anatomical variation of having a single portio vaginalis uteri into which both cervices converge presented a distinct challenge during this procedure. Intraoperatively, the sentinel lymph nodes on both sides demonstrated intense staining, which facilitated their identification (Fig. 5). Macroscopically, the ICG-positive lymph nodes appeared inconspicuous. Frozen section examination was conducted and confirmed one tumor-free lymph node on each side (0/2 sentinel lymph nodes). Further comprehensive pelvic lymphadenectomy was omitted in accordance with current guidelines. In order to prevent ureteral injury during the subsequent surgery, a ureteral splint was inserted on the right side. Laparotomic hysterectomy with salpingectomy and resection of parametrial and paracervical tissue as well as the proximal third of vagina (according to Piver type II) was performed (Figs. 4 and 6). The adhesions in the area of the uterine horns were successfully removed without injuring the ureter. The uterine arteries were transected at their origin from the internal iliac arteries. An oophoropexy was performed by suturing the ovaries, pedicled at their vessels, to the pelvic wall above the psoas muscle and placing them in the abdominal cavity to position them outside the radiation field, in anticipation of a potential need for postoperative radiotherapy. The surgery also included intraoperative lavage for cytological examination which revealed no abnormal findings. Furthermore, no residual

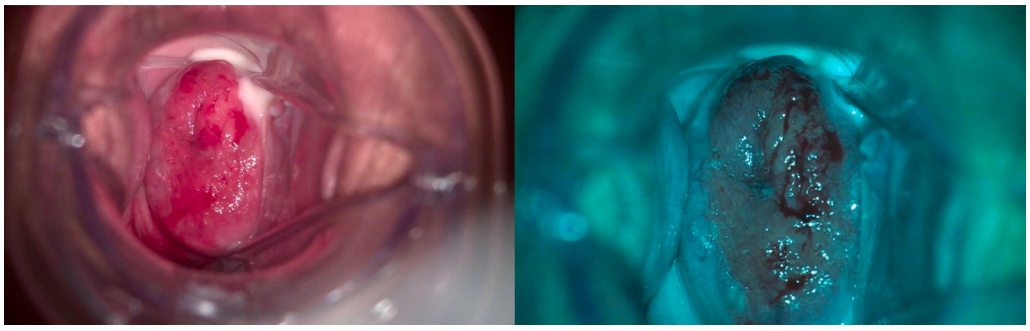

Fig. 1. Native (a) and green filter (b) colposcopy revealing a partly polypous altered portio vaginalis uteri with a highly vulnerable ectopia before application of acetic acid solution. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

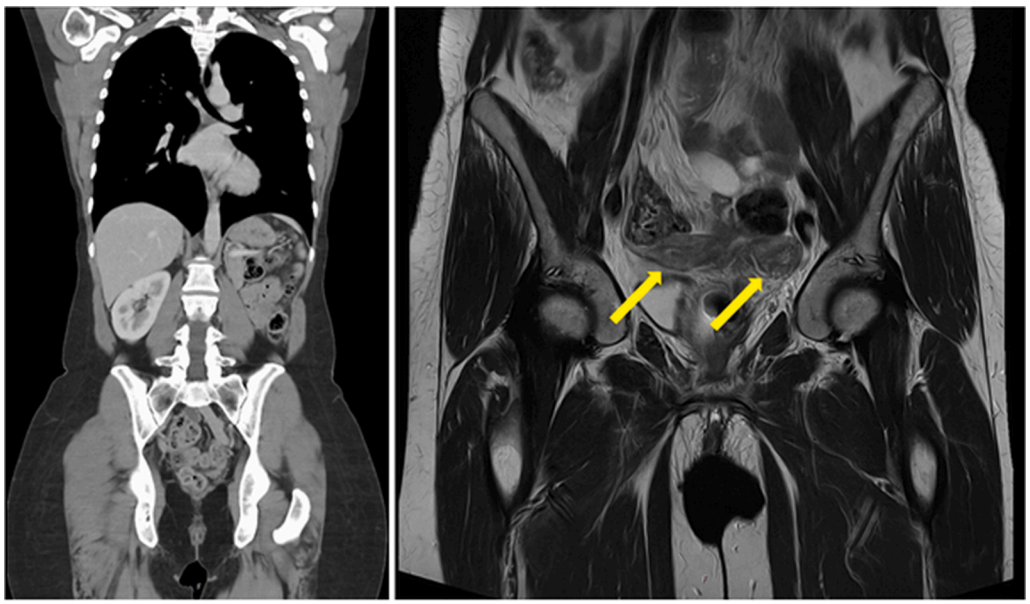

Fig. 3. a. Computed tomography (CT) of the thoracic, abdominal and pelvic area, revealing renal agenesis on the left side. b. Magnetic resonance imaging (MRI) of the pelvis, revealing two uterine horns.

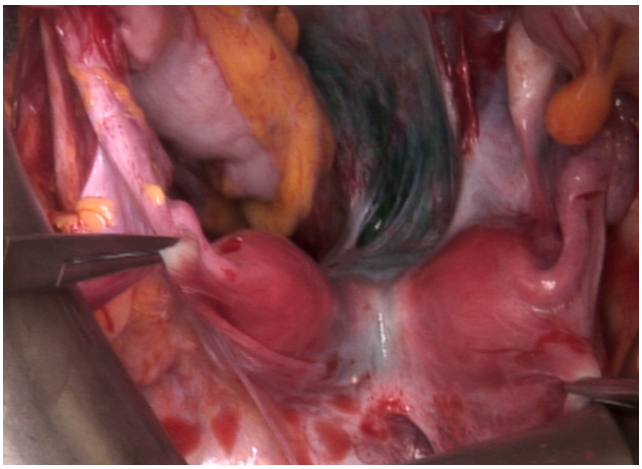

Fig. 4. Situs during laparotomy: intraoperative finding of two separate uterine horns, consistent with a uterus didelphys.

components of the known cervical carcinoma were identified in the histopathological analysis of the hysterectomy specimen. Merely low-grade squamous cell dysplasia, consistent with a CIN I/ low grade squamous intraepithelial lesion (LSIL), was detected in the area of the portio vaginalis uteri. The fallopian tubes were also found to be histologically cancer-free. The definitive histopathological assessment of the lymph nodes, including immunohistochemical ultrastaging with pan-cytokeratin staining, showed no evidence of tumor infiltration. The embedded residual tissue from the sentinel lymphadenectomy on the right side revealed an additional small lymph node, which was found to be unremarkable. In conjunction with the histological findings of the cone biopsy, final TNM stage was pT1b1 pN0 (0/3, 0/2 sentinel lymph nodes) L0 V0 Pn0 G2 R0. The postoperative recovery proceeded without complications and the patient was discharged from the hospital after five days. Six weeks postoperatively following the Piver type II procedure, the ureteral splint on the right side was successfully removed. The patient was referred for regular aftercare. No abnormal findings were found in the two follow-up-examinations carried out to date.

3. Discussion

Cervical carcinoma is one of the most common types of cancer in women worldwide, with an estimated 604,000 new cases in the year of 2020, and the incidence of genital malformations among the female populace spans from 0.2 to 6.7 % (Kiblboeck et al., 2023; Sung et al., 2021). Nonetheless, cervical carcinoma in women with a Müllerian malformation represents a rarity (Cordoba et al., 2017; Matylevich et al.,

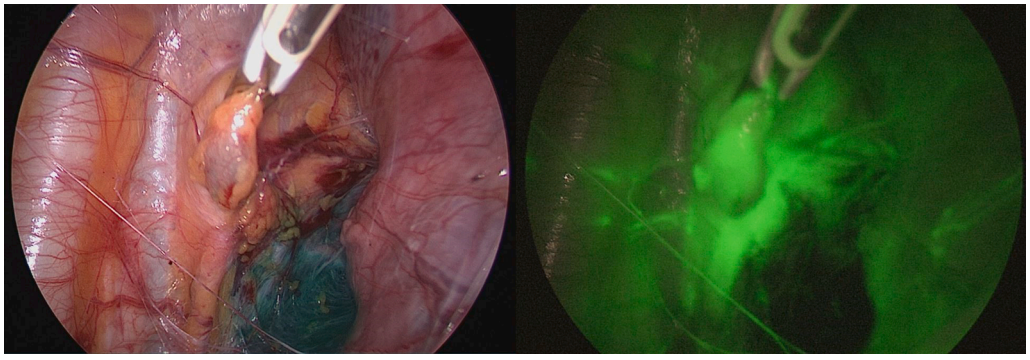

Fig. 5. Identification of the sentinel lymph node in the pelvic lymphatic drainage area, natively (a) and with the aid of indocyanine green fluorescence (b). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

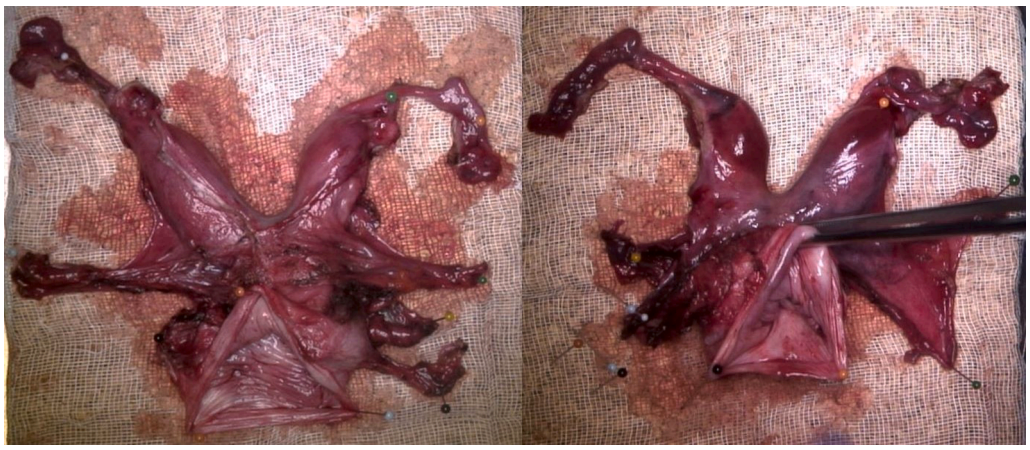

Fig. 6. Hysterectomy specimen with fallopian tubes, parametria and proximal vaginal cuff.

2022; Mabuchi et al., 2022; Lei et al., 2021; Lei et al., 2020; Zong et al., 2019; Kusunoki et al., 2018; Kaneyasu et al., 2019). Although the available literature predominantly comprises only individual case descriptions, various histopathological subtypes of cervical carcinoma have already been documented in association with genital anomalies (Zong et al., 2019). Interestingly, urinary tract malformations were often associated with adenocarcinoma (Lei et al., 2020; Zong et al., 2019). It should be emphasized that this observation is based on a small cohort, leaving the validity of a causal connection in question.

Müllerian malformations may impede cancer detection due to atypical symptoms or challenges performing certain diagnostics. In the present case for example, the two separate cervical canals were not visible in the speculum examination as they led to a common portio vaginalis uteri. Further anatomical anomalies limiting accessibility for clinical assessments as well as procedures like biopsy sampling include obstruction of a uterine cervix or vaginal septa (Zong et al., 2019; Kusunoki et al., 2018; Kaba et al., 2013). The experience of discomfort or even pain during examination of the pelvic area also impairs diagnostics and can affect patients with Müllerian malformation to a special extent (Lei et al., 2020; Kaneyasu et al., 2019).

In the present case, the patient received guideline-compliant curative treatment with laparotomic hysterectomy according to Piver type II following a staging laparoscopy with sentinel lymphadenectomy. A particular challenge was the injection of ICG into the cervical stroma of both cervices, given the patient's anatomical variation of having a single portio vaginalis uteri into which both cervices converge. Despite the anatomical deviation, bilateral staining of the sentinel lymph nodes was successfully achieved without difficulty. No complications occurred during the surgery, and to date, there is no indication of cancer recurrence. However, surgical therapy carries particular risks for patients with Müllerian malformations. Especially in cases of urinary tract anomalies, the healthy ureter has to be diligently protected (Lei et al., 2020; Kusunoki et al., 2018). For the presented patient, it was decided to insert a protective ureteral stent to mitigate the risk of ureteral injury during the surgery.

For patients with advanced cervical carcinoma requiring irradiation, individualized radiotherapy is necessary to meet the anatomical peculiarities of the genital anomaly (Cordoba et al., 2017; Lei et al., 2021; Kaneyasu et al., 2019). Choosing the right applicator, for example, represents a major challenge since not all areas are amenable to commercial applicators in patients with Müllerian malformations (Cordoba et al., 2017; Lei et al., 2020; Kaneyasu et al., 2019). The target area design can also be very complex (Lei et al., 2021; Lei et al., 2020; Kaneyasu et al., 2019).

4. Conclusion

The current case demonstrates the successful implementation of guideline-compliant therapy for early-stage cervical cancer in an individual with Müllerian malformation. Nonetheless, particular heed must be paid to anatomical peculiarities. This is especially crucial in instances of concomitant urinary tract anomalies, where protective measures are imperative to safeguard normal kidney function.

Authors' contributions

The first draft of the manuscript was written by Annika Krückel and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Annika Krückel: Writing – original draft. **Miriam Saatze:** Writing – review & editing. **Annika S. Behrens:** Writing – review & editing. **Matthias W. Beckmann:** Writing – review & editing. **Patrik Pöschke:** Writing – review & editing. **Julius Emons:** Writing – review & editing, Supervision.

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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References

Cordoba, A., Escande, A., Comte, P., Fumagalli, I., Bresson, L., Mubiayi, N., Lartigau, E., 2017. Locally advanced adenocarcinoma of the cervix on uterus didelphys: a case report. J. Contemporary Brachyther. 9 (1), 71–76. https://doi.org/10.5114/jcb.2017.65640.

e Passos, I.d.M.P., Britto, R.L., 2020. Diagnosis and treatment of müllerian malformations. Taiwan. J. Obstet. Gynecol. 59 (2), 183–188. https://doi.org/10.1016/j.tjog.2020.01.003.

Kaba, M., Gungor, T., Baser, E., Ozdal, B., Sirvan, L., 2013. Cervical cancer in a patient with uterus didelphys and obstructive hemivagina, ipsilateral renal anomaly (OHVIRA) syndrome. Arch. Gynecol. Obstet. 288, 229–230. https://doi.org/10.1007/s00404-012-2690-y.

Kaneyasu, Y., Koh, I., Fujiwara, H., Hirata, E., Kudo, Y., Arihiro, K., Miharu, N., Nakagawa, T., Takahashi, I., Takeuchi, Y., 2019. Concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of the cervix in a uterus didelphys with vaginal septum. J. Contemporary Brachyther. 11 (2), 180–188. https://doi.org/10.5114/jcb.2019.84506.

Kiblboeck, S., Oppelt, P., Oppelt, P., Stein, R., Ommer, S., Pavlik, R., Rall, K., Kongrtay, K., Wagner, H., Hermann, P., et al., 2023. Can Classifications Adequately Represent Genital Malformations?: EVA Study (E SHRE/ESGE | V CUAM | A FS) - A Prospective Multicenter Study to Evaluate the Current Female Genital Malformation Classifications. Geburtshilfe Frauenheilkd 83 (7), 827–834. https://doi.org/10.1055/a-2043-9982.

Kusunoki, S., Huang, K.-G., Magno, A., 2018. Laparoscopic en bloc resection of a para-cervical cancer with OHVIRA syndrome. Taiwan. J. Obstet. Gynecol. 57 (1), 141–143. https://doi.org/10.1016/j.tjog.2017.12.024.

Lei, C., Huang, M., Li, N., An, J., Xiong, S., Li, X., Wu, L., 2020. IMRT and HDR-ICBT for locally advanced clear cell adenocarcinoma of the cervix in uterus didelphys associated with unilateral renal agenesis. Front. Oncol. 10, 1136. https://doi.org/10.3389/fonc.2020.01136.

Lei, C., Huang, M., Li, N., An, J., Xiong, S., Xu, Y., 2021. Intensity-modulated radiotherapy combined with intracavitary brachytherapy for locally advanced cervical cancer with uterus didelphys. Gynecol. Oncol. Rep. 36, 100724 https://doi.org/10.1016/j.gore.2021.100724.

Mabuchi, S., Hayashida, H., Kubo, C., Takemura, M., Kamiura, S., 2022. Herlyn-Werner-Wunderlich syndrome (HWWS)-associated gynecological malignancies: A case report and literature review. Gynecol. Oncol. Rep. 43, 101051 https://doi.org/10.1016/j.gore.2022.101051.

Matylevich, O.P., Schmeler, K.M., Gemer, O., Petukhou, V.S., Kopschaj, P.A., 2022. High-grade cervical dysplasia in a woman with uterine didelphys: A case report. Gynecol. Oncol. Rep. 42, 101027 https://doi.org/10.1016/j.gore.2022.101027.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F., 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 71 (3), 209–249. https://doi.org/10.3322/caac.21660.

Zong, L., Wang, W., He, Y., Cheng, N., Xiang, Y., 2019. Carcinoma of the lower female genital tract in patients with genitourinary malformations: a clinicopathologic analysis of 36 cases. J. Cancer 10 (13), 3054. https://doi.org/10.7150/jca.30486.