Case Report

Unlucky Combination: A Report on Two Cases of Herlyn-Werner-Wunderlich Syndrome

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ABSTRACT: Herlyn-Werner-Wunderlich (HWW) syndrome, currently known as Obstructed Hemivagina and Ipsilateral Renal Agenesis (OHVIRA), is a rare congenital Mullerian abnormality defined by a triad of didelphic uterus, obstructed hemivagina, and ipsilateral renal agenesis. It affects approximately 0.1-3.8% of women worldwide. This paper discusses two cases of HWW syndrome managed in a private tertiary hospital highlighting the spectrum of signs and symptoms of the disease. It is hoped that this study will inform practitioners and patients about the various presentations and the management of OHVIRA.

Keywords: *Herlyn-Werner-Wunderlich syndrome; ipsilateral renal agenesis; Mullerian duct anomalies; obstructed hemivagina; uterine didelphys*

INTRODUCTION

Congenital Mullerian duct fusion abnormalities are conditions that affect the female reproductive system, specifically the uterus, cervix, fallopian tubes and superior aspect of the vagina. Mullerian anomalies affect 0.1% - 3.5% of females based on retrospective and observational studies.[1] The most common abnormality is a bicornuate uterus comprising 37% of all reported uterine anomalies.[2]

The Herlyn-Werner-Wunderlich (HWW) syndrome is a rare combination of a didelphic uterus, obstructed hemivagina, and ipsilateral renal agenesis. There are no studies mentioning the prevalence of HWW syndrome in the Philippines. However, review of Philippine literature revealed nine reported cases of HWW syndrome.[3,4] In our institution, there has only been one reported case.[5] The incidence found in international literature is 1 in 2000 to 1 in 28,000.[6] The patients with this rare condition usually present with menstrual problems, (amenorrhea, severe dysmenorrhea or intermenstrual spotting) and a palpable mass in the vagina due to accumulation of blood, mucus, or rarely, pus.[7,8] Delay in its diagnosis and management is inevitable due to its rarity; however, the complications can be devastating. The patients with this condition can suffer from endometriosis, ovarian endometrioma, upper genital tract infection, pelvic adhesions, ectopic pregnancy, recurrent pregnancy loss, and infertility.[9] This paper describes two patients with HWW syndrome with different characteristics and management. The first case shows the ideal approach to young patients with Mullerian abnormalities. The second case describes a patient who had several opportunities for early diagnosis. Despite treatment, this patient still showed the long-term complications of HWW syndrome. This study aimed to increase awareness regarding Mullerian anomalies, discuss the ideal diagnostic tools and management for HWW syndrome, and promote early diagnosis and treatment to avoid complications.

CASE REPORT

Case 1

An 18-year old nulligravid with history of sexual contact presented with left lower quadrant pain. The patient has been regularly menstruating since she was 13 years old, lasting for four to five days, consuming four pads per day, fully soaked, with occasional dysmenorrhea. Three months prior to admission, the patient noted sudden onset of left lower quadrant pain not associated with menstruation but with intermenstrual bleeding. Pregnancy test was negative. Increasing severity of the pain prompted consult with an obstetrician-gynecologist. On physical examination, she had normal external genitalia. Speculum exam revealed a 2x2 cm bulge on the superior third of the left lateral vaginal wall with a pink, smooth cervix without erosions and polyps. Internal examination revealed a 2 x 2 cm, slightly tender, movable mass at the superior third of the left lateral vaginal wall. The cervix was firm, long, and closed, without cervical motion tenderness. The uterus was not enlarged and nontender, but there was fullness in the left adnexa with minimal tenderness on deep palpation. There was no right adnexal mass or tenderness. A 2D transvaginal ultrasound was requested which showed uterine didelphys with hematocolpos in the left hemiuterus. The left cervix was dilated to 5.80 x 3.83 x 5.19 cm, fluid-filled, with heterogenous echoes approximately 14.59 ml. There was a left adnexal mass measuring 4.17 x 1.90 x 3.31 cm suggestive of pyosalpinx or hematosalpinx. At the upper third of the vagina, there was an echogenic band 1.37 cm away from the cervix measuring 0.3 cm, a longitudinal vaginal septum confirmed by 3D ultrasound. She was referred to a reproductive endocrinology and infertility specialist who requested a kidney and urinary bladder ultrasound which revealed an absent left kidney and normal sized right kidney. Renal function was normal. Resection of the longitudinal vaginal septum followed by diagnostic hysteroscopy was done (Figure 1). Intraoperative findings revealed 50 ml of chocolate-like fluid drained from the left upper vagina.

No hematometra was noted in the left hemi-uterus. Postoperative course was unremarkable. On follow-up one week after the surgery, there was resolution of the left lower quadrant pain and intermenstrual bleeding.

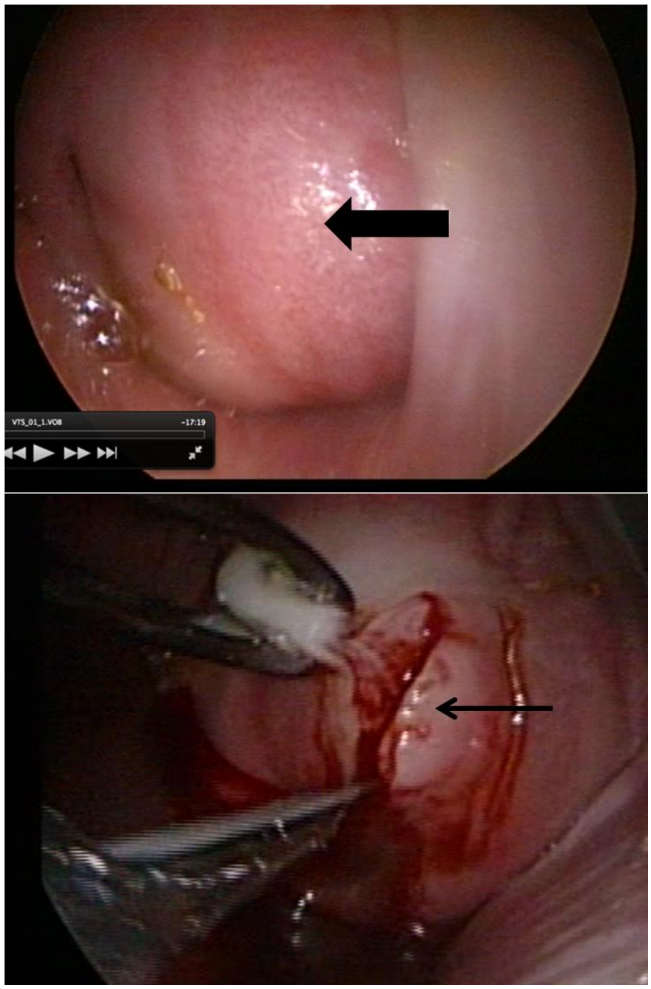

Figure 1. Intraoperative images showing the longitudinal vaginal septum (thick arrow) and resection of the septum (thin arrow).

Case 2

A 37-year old nulligravid with history of sexual contact and right kidney agenesis since childhood, presented with abnormal uterine bleeding. At the time of diagnosis of kidney agenesis, no workup for gynecologic abnormality was done. Renal biopsy of the left kidney showed focal segmental glomerulosclerosis. She was initially treated with prednisone but she eventually developed end stage renal disease and was started on dialysis six years ago. The patient had been suffering from severe dysmenorrhea and irregular menstruation since 15 years old. Her menses occur at three to six-month intervals, lasting for four to nine days, consuming six pads per day, moderately soaked. She denied other symptoms. At 22 years old, the patient consulted a gynecologist and was diagnosed with an ovarian cyst. She underwent unilateral oophorocystectomy. After one year, she transferred to another gynecologist due to the persistence of symptoms. A transvaginal ultrasound was done which showed didelphic uterus and an obstructed right hemivagina. The patient allegedly underwent hysteroscopy with removal of the obstruction. There was resolution of the dysmenorrhea but irregular menstruation persisted. No medical management was offered to the patient. In the interim, there was occasional mild dysmenorrhea.

Six years prior to admission, she was diagnosed with breast cancer, left, stage IIB. She underwent lumpectomy, 28 cycles and five boosters of radiotherapy, and Tamoxifen therapy for four years.

On presentation and upon physical examination, she had normal external genitalia. Speculum exam showed a pink and smooth cervix with minimal non foul-smelling brownish discharge, without erosions or polyps. Internal exam revealed a long, firm, closed cervix, without motion tenderness. Both hemiuteri were enlarged to 12 weeks size, nontender with no noted adnexal mass or tenderness. Rectovaginal exam showed tight sphincteric tone, intact rectal vault and rectovaginal septum. Transvaginal ultrasound was done which showed uterine didelphys, single cervix with two cervical canals and two vaginas, the right hemivagina obstructed in the middle third with a septum. No hematometra or hematocolpos was noted.

Upon exploration, both hemiuteri were densely adherent to the sigmoid colon and anterior abdominal wall. The right ovary and fallopian tube were densely adherent to the pelvic sidewalls. The left ovary was cystically enlarged and multiloculated measuring 5.5 x 5.0 x 2.0 cm, exuding clear fluid upon rupture. The right endometrial cavity exuded chocolate brown fluid upon opening, with note of smooth endometrium. The right cervix appeared to be obliterated. The patient underwent total abdominal hysterectomy with bilateral salpingooophorectomy and adhesiolysis. Histopathology revealed uterine didelphys, leiomyoma in the right hemiuteri, secretory endometrium, endometriosis in the right ovary and fallopian tube, and endometriotic cyst, left ovary (Figure 2). The patient tolerated the procedure well and no complications were noted. Postoperatively, there were no immediate complications but on follow-up with patient one year after surgery, there was noted postmenopausal symptoms such as vaginal dryness and hot flushes. The patient was initially offered menopausal hormone therapy but was lost to follow-up.

DISCUSSION

Herlyn-Werner-Wunderlich syndrome was first described by Purslow in 1922 and was first named as a syndrome of obstructed hemivagina, uterus didelphys, and ipsilateral renal agenesis in 1971.[11,12] The development of the mullerian and renal system occurs side by side at the same time. The possible etiology of the HWW syndrome is thought to be due to a disruption in the development of the caudal portion of one mesonephric duct with secondary

involvement of the ipsilateral Mullerian duct. This affects the normal ureteric budding and kidney differentiation in one side leading to renal agenesis and abnormal location of the ipsilateral Mullerian duct. Due to this, the abnormal Mullerian duct fails to combine properly with its counterpart leading to a double uterus and an obstructed cervical or vaginal canal.[13,14]

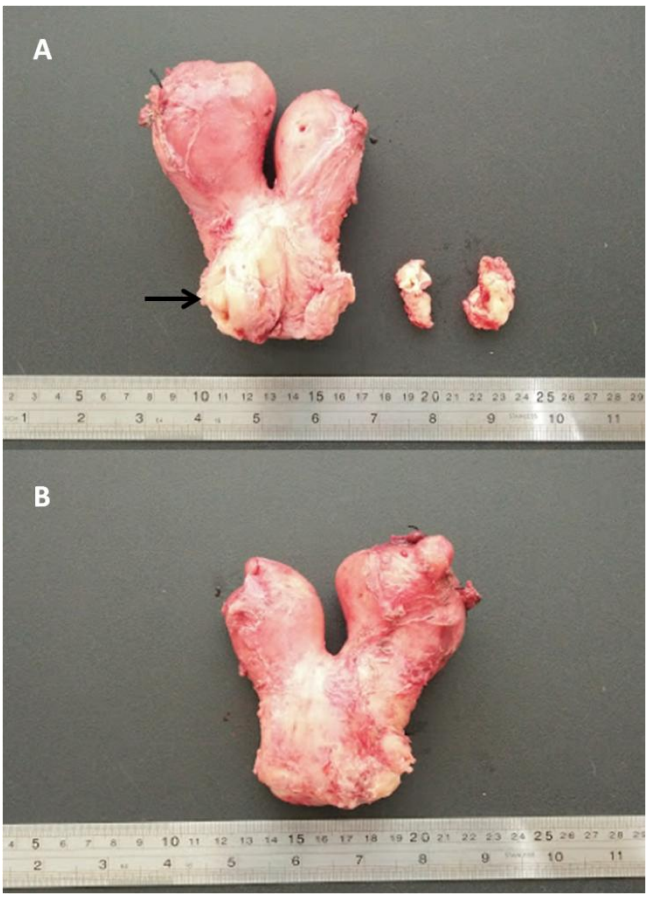

Figure 2. Uterus didelphys (A) anterior view (B) posterior view with leiomyomata in the right hemiuterus (arrow).

The most widely used Mullerian anomaly classification system is that of the American Society for Reproductive Medicine (ASRM) (Table 1).[1] Patients with didelphic uterus or those with complete or partial duplication of the vagina, cervix, and uterus are classified under Class III. There are several classification schemes for Mullerian anomalies such as the ESHRE/ESGE (European Society of Human Reproduction and Embryology) but the ASRM classification is the most widely accepted since it organizes anomalies according to the major uterine anatomic defect allowing standardized reporting of cases. However, one of its limitations is that some complex conditions such as HWW syndrome cannot be included in the classification system because of the lack of categories for cervico-vaginal and genitourinary anomalies.[1]

Table 1. AFS/ASRM Classification of Congenital Anomalies of the Female Genital Tract.

Classification	Uterine anomaly	Associated Anomalies
Class I	Hypoplasia and agenesis	(a) Vaginal (b) cervical (c) fundal (d) tubal
Class II	Unicornuate	(a) communicating (b) noncommunicating (c) no cavity (d) no horn
Class III	Didelphys	
Class IV	Bicornuate	(a) partial (b) complete
Class V	Septate	(a) partial (b) complete
Class VI	Arcuate	
Class VII	Diethylstilbesterol drug-related	

Patients who have HWW syndrome are usually asymptomatic until menarche. Most commonly, they present with severe and progressive dysmenorrhea, as well as irregular menstruation and intermenstrual spotting. Most patients who have these symptoms are those with microperforation or a small communication between the obstructed and non-obstructed side, signifying accumulation of menstrual blood in the obstructed hemiuterus or hemicervix then gradual drainage through the perforation.[7,8] However, these symptoms may be misdiagnosed as pelvic endometriosis, delaying important workup such as kidney and urinary bladder ultrasound. These patients may also have fertility problems such as spontaneous abortion in 40% of cases, most probably due to the uterine malformation.[14] On physical examination, a tender suprapubic or abdominal mass may be felt and this may be caused by a hematometra. One the other hand, a hematocolpos may present as a paravaginal or paracervical cystic mass, as seen in the first case. Both cases presented with dysmenorrhea but the second patient presented with more severe symptoms including irregular menstruation. Ironically, it was the second patient who was diagnosed late, probably because the first patient presented with acute symptoms, prompting gynecologic consult immediately.

Delay or misdiagnosis of Mullerian abnormalities can have serious consequences in the upper genital tract such as endometriosis, hematosalpinx, and pelvic adhesions.[8] Possible pathogenesis of these conditions is retrograde menstruation caused by the obstruction. Rarely, infection in the lower vaginal tract may ascend to the upper genital tract causing pyocolpos or pyosalpinx.[6]

The gold standard for diagnosing Mullerian anomalies is the combination of hysterosalpingogram (HSG) and laparoscopy.[19] The imaging of choice in Mullerian anomalies is an MRI (especially T2-weighted imaging) due to its accuracy and better resolution in delineating soft tissue such as the uterus and vagina.[16] However, due to multiple reasons such as availability, accessibility, lower radiation exposure, and cost, ultrasonography is usually done prior to other diagnostic tests. Three-dimensional ultrasound and MRI were found to have a high degree of concordance, and 3D ultrasound was also found to be as accurate as hysteroscopy and

laparoscopy.[17,18] Hence, it is recommended to use a 2D-Ultrasound as screening test and a 3D-ultrasound to serve as a definitive diagnostic test.[1]

Surgical and medical management for HWW syndrome aim to provide symptomatic relief, prevent complications, and maximize the fertility of a patient.[1] For patients with symptomatic obstructed hemivagina, resection of the vaginal septum with marsupialization is the procedure of choice rather than simple incision and drainage because the former is associated with less infection and re-occlusion.[6,7] Simultaneous laparoscopy is not routine for cases of HWW syndrome unless a hematosalpinx or ovarian endometrioma are found on imaging.[6] After surgery, the next step is to suppress menstruation using various medications such as combined oral contraceptive pills, progesterone or GnRH analogs to prevent re-accumulation of menstrual blood.[6]

The incidence of breast cancer in patients with Mullerian anomalies is unknown and no case has been reported in the Philippines. In one foreign study, only two cases of patients with uterine didelphys and breast cancer who underwent tamoxifen therapy were mentioned.[20] Both patients eventually developed endometrial cancer.

The importance of having a high index of suspicion for Mullerian anomalies in the presence of renal abnormalities cannot be overly emphasized. Early intervention is pertinent in order to prevent complications and enhance a patient's chances of reproduction. Despite having a higher rate of spontaneous abortion, the live birth rate of patients with HWW syndrome can be as high as 91% if obstruction is treated.[21] A referral to a nephrologist is also prudent for monitoring of the remaining kidney function. A multidisciplinary team composed of an obstetrician-gynecologist, radiologist, psychologist, nephrologist, and fertility specialist is definitely needed in dealing with patients with HWW syndrome.

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