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Mayer-Rokitansky-Kuster-Hauser Syndrome with Hyperandrogenemia: A Rare Case of Mullerian Dysgenesis

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A B S T R A C T

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome with hyperandrogenism is a variety of Müllerian duct anomalies categorized by congenital aplasia of uterus and upper part two third of the vagina usually associated with uncommonly high level of testosterone. The MRKH affects 1 out of 4500 women and it is the most common causes of primary amenorrhea, however there are only 4 cases reported of MRKH syndrome with hyperandrogenemia in literature2. The MRKH syndrome usually remains asymptomatic up until the patient complains with primary amenorrhea nonetheless with normal secondary sexual physical development. We reported a case of a 21-year-old female with MRKH syndrome with hyperandrogenism who presented with primary amenorrhea, physical examination include tanner stage 5 breasts, short vaginal canal, pubic hair stage 4 with absence of cervix, and no clitoromegaly. Transvaginal ultrasound shows an infantile uterus while MRI shows small uterus with inactive endometrium with an incidental findings of Tarlov cyst. Counseling, assurance and supportive psychotherapy were given to the patient. Follicle stimulating hormone, chest X-ray, 75 gram oral glucose tolerance test, BUN, creatinine, audiogram and electrocardiogram results were reported with normal ranges. Chromosomal analysis was 46 XX karyotype. Serum testosterone was markedly elevated at 11.1 nmol/L, above the normal values for female.

1. Introduction

Mullerian dysgenesis is defined as the absence or hypoplasia of Mullerian duct-derived structures, which include the upper two-thirds of the vagina, uterus, fallopian tubes, and uterus. Congenital impairment of the uterus and vagina, also known as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, constitutes the most common clinical syndrome of Mullerian dysgenesis. It is the second most common reason for primary amenorrhea following gonadal dysgenesis.[1]

The MRKH was first described in 1829 by Mayer, in 1838 by Rokitansky, in 1910 by Kuster, and in 1961 by Hauser and Schreiner.[2] On the other hand, MRKH with hyperandrogenism was described in 2011 by Biason Lauber et al., where they investigated four 46, XX adolescent females with Mayer-Rokitansky-K€uster-Hauser syndrome and hyperandrogenism. Molecular analysis of the WNT4 gene permitted us to identify a new mutation.[3] Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is an uncommon disorder with an estimated incidence of approximately 1 per 4500 - 5000 females however, only 4 cases were reported of MRKH syndrome associated with hyperandrogenemia in literature.[4] Patients with MRKH syndrome become characteristic during their late puberty, with primary amenorrhea as their complaint. General MRKH is divided into two categories: MRKH type 1 and MRKH type 2. MRKH type 1 is reported for approximately 44% of cases. The typical form is by the

involvement of the caudal part of the Mullerian duct without any associated malformations. MRKH type 2 is the atypical form and is the most common form of MRKH, recorded for approximately 56% of cases. It is associated with additional malformations generally affecting the renal and skeletal systems.[4] The worst form of MRKH type 2 is MURCS (Mullerian duct aplasia, unilateral renal agenesis and cervicothoracic somite anomalies) syndrome which accounts for 16%.[4] In the registry of Philippine Obstetrical and Gynecological Society, there is no reported case yet of MRKH with hyperandrogenemia, thus, making this case the first reported in the Philippines and fifth in the literature as to the time of writing this paper. This paper presents a case of a 21-year old female who came in due to primary amenorrhea and infertility. Physical examination findings include Tanner stage 5 breasts, infantile uterus with short vaginal canal and no clitoromegaly. Upon work-up, a female karyotype was noted with findings of hyperandrogenemia and Tarlov cyst. The following are our objectives: To present a case of MRKH syndrome with hyperandrogenemia, to discuss the pathophysiology, diagnosis and management options for MRKH syndrome with hyperandrogenemia, and to recognized the percentage of possibilities of another anomalies that are presence in the affected family.

2. Case Presentation

A 21 year old woman consulted at our institution due to primary amenorrhea and primary infertility. She is phenotypically female who had breast budding at 10-16 years old. By 18 years of age, patient consulted a physician due to primary amenorrhea in the family and was advised to await her menarche. Patient is married for four years and has been trying to conceive thus she consulted at our institution.

Past medical history was unremarkable. There were no hereto-familial diseases noted such as hypertension, diabetes, asthma, cancer, thyroid and kidney diseases. There was no history of sexual ambiguity, sterility or primary amenorrhea. The patient is the seventh in a brood of eight. There are 6 boys and 2 girls in the family. Her sister is married with children and has no menstrual difficulties such as dysmenorrhea or abnormal uterine bleeding. Their youngest male sibling is still unmarried. Patient is a non-smoker, a non-alcoholic beverage drinker and is currently unemployed. Coitarche was at 17 years old with one sexual partner and is currently in a monogamous relationship. She has no history of any contraceptive use. No other sexual difficulties such as dyspareunia, vaginismus, arousal and orgasm problems. The patient also has no complaints of cyclic pelvic pain.

On physical examination, the patient has a height of 160 cm with lean and long limbs and a BMI of 18.35 kg/m^2. Vital signs were stable with no acne nor laryngeal prominence. There was no hirsutism with Modified Ferriman-Gallwey score of 1. There was axillary hair and her breasts were fully developed and grossly normal at Tanner stage V (Figure 1).

Examination of the patient's external genitalia revealed pubic hair at Tanner stage IV, normal-looking clitoris, labia major and minor and a small urethral opening (Figure 2a-c). Speculum examination showed a pinkish smooth vaginal mucosa, vaginal canal measured 4 cm and the vagina ended in a blind pouch with no appreciable cervix, no abnormal vaginal discharge or vaginal bleeding (Figure 2d). On internal examination, the vagina admits two fingers with ease, vaginal canal measures 4 cm with no palpable cervix, uterus nor adnexae. Rectovaginal examination confirmed it with internal examination findings.

Transvaginal ultrasound revealed absence of cervix with small homogenous structure (uterus) seen at the midline (2.19 x 2.41 x 1.26 cm in size). The right ovary was normal in size and echotexture with a small dense area (1.01 x 1.02 cm in size). Impression: Infantile uterine corpus, dermoid focus, right ovary, normal left ovary (Figure 3).

Pelvic and abdominal magnetic resonance imaging revealed a small uterus measuring 40 x 21 x 17 mm with endometrial thickness of 7.6 mm. No cervix was

seen and the ovaries were normal. Although the visualized osseous structures are unremarkable, a small midline cyst measuring 18 x 16 x 11 mm was seen posterior to the S2 vertebra body. Impression: Mullerian agenesis specifically Mayer Rokinstansky Kuster Hauser syndrome, Tarlov cyst, S2.

Follicle stimulating hormone, chest X-ray, 75 gram oral glucose tolerance test, BUN, creatinine, audiogram and electrocardiogram results were normal. Serum testosterone was 11.1 nmol/L, above the normal values for both male and female (Table 1). Chromosomal analysis was 46 XX karyotype (Figure 4).

Table 1. Test Results from Possible MRKH case.

Test type	Result	Normal value
Bun	2.70 mmol/L	1.7- 8.3 mml/L
Creatinine	58.00 umol/L	44.2 – 150.3 umol/L
Tsh	0.929 µIU/ml	0.27 – 3.75 µIU/ml
Fsh	5.6 mIU/ml	- ovulatory peak 4.0 – 13.5 mIU/ml - pre and post ovulatory 0.5 – 9.5 mIU/ml - postmenopausal 30-135 mIU/ml
Testosterone	**11.1 nmol/L**	0.9 – 4.5 nmol/L
75g OGTT	FBS 4.73 mmol/L 1 hour 8.02 mmol/L 2 hours 4.96 mmol/L	FBS : 4.2 – 6.4 mmol/L 1 hour: 6.6 – 9.35 mmol/L 2 hours : 3.81- 6.6 mmol/L
Audiogram	Normal findings	
ECG	Normal axis	
Chest X-ray	No significant pulmonary findings	

The diagnosis of MRKH syndrome was disclosed to her and husband. Counseling was done with emphasis on persistence of amenorrhea and progressive vaginal dilatation if the need arises. She was also instructed to watch out for signs and symptoms of endometriosis such as cyclic pelvic pain or pelvic masses. The occurrence of such will warrant hysterectomy by laparoscopy.

Upon follow-up, the patient reported decreased sexual satisfaction with absence of orgasm and had periods of depression after initial disclosure of the diagnosis. The couple was then educated on pelvic anatomy and advised modifications in sexual behavior so as to attain mutual sexual satisfaction. Emphasis was also made on her role as a wife and a female capable of normal satisfactory sexual and interpersonal relationships. Referral to Psychiatry Department was also done for supportive psychotherapy.

As all patients with Mayer Rokitansky Kuster Hauser syndrome lack a functional uterus, the couple's desire for fertility was addressed by informing them that the chance for having a biological child is possible through assisted reproductive technology (ART) with gestational surrogacy unfortunately surrogacy in the Philippines is still not ethical unless they went abroad. Adoption and uterus transplantation were also discussed.

Upon follow-up after five months, the patient has no complaints on dyspareunia, vaginismus, arousal and orgasm problems and cyclic pelvic pain. She is contemplating adoption since ART with surrogacy and uterus transplantation are not feasible for them due to financial constraints.

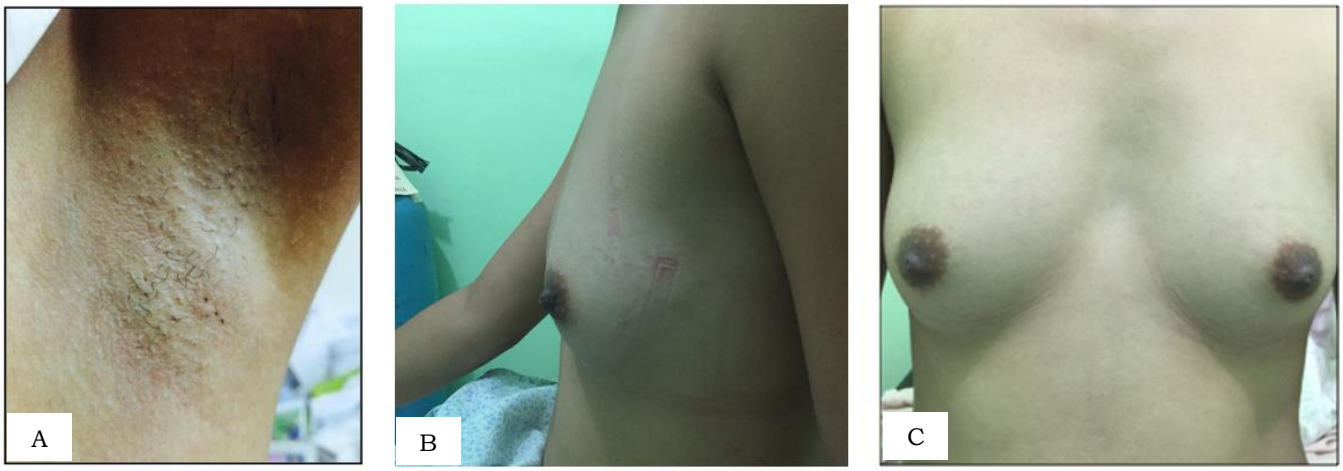

Figure 1. There was axillary hair and her breasts were fully developed and grossly normal at Tanner stage V; Left to right: a) Normal Axilla hair; b) Fully developed breasts; c) Fully developed breasts at Tanner V.

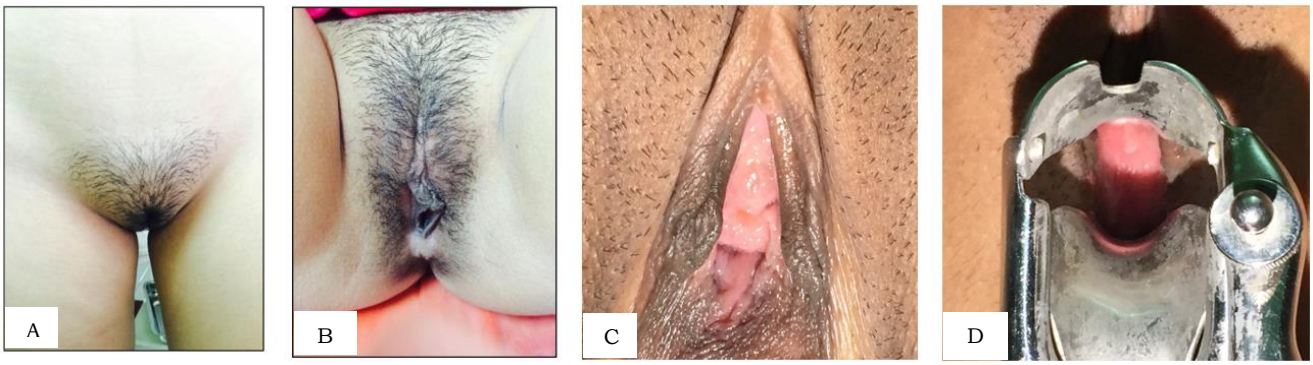

Figure 2. Examination of the patient's external genitalia revealed pubic hair; Left to right: a) Pubic hair at Tanner IV; b) Pubic hair at Tanner IV with normal-looking clitoris, labia majora and labia minora; c) Normal-looking clitoris, labia majora and labia minora; d) Vaginal canal of 4 cm ending in a blind pouch.

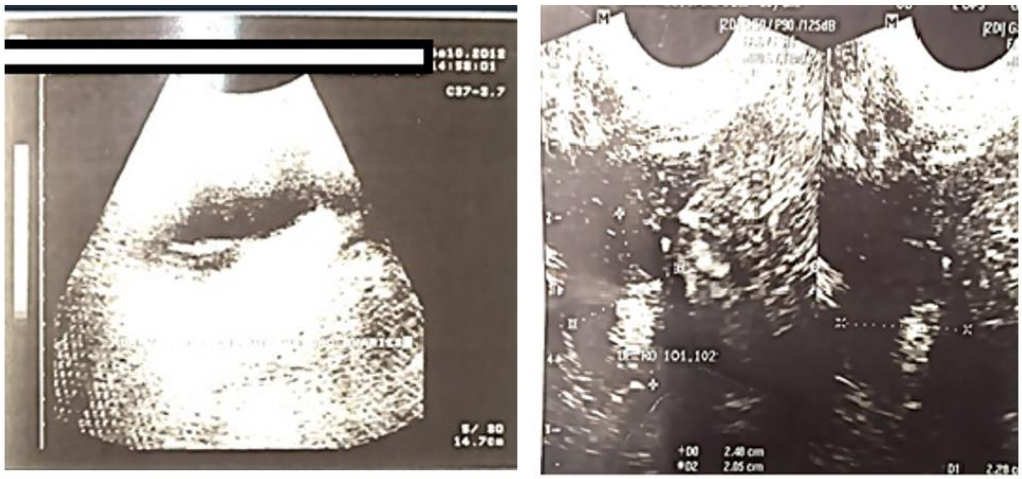

Figure 3. Ultrasound shows infantile uterus (Left); Ultrasound shows small homogenous structure seen at the midline (Right).

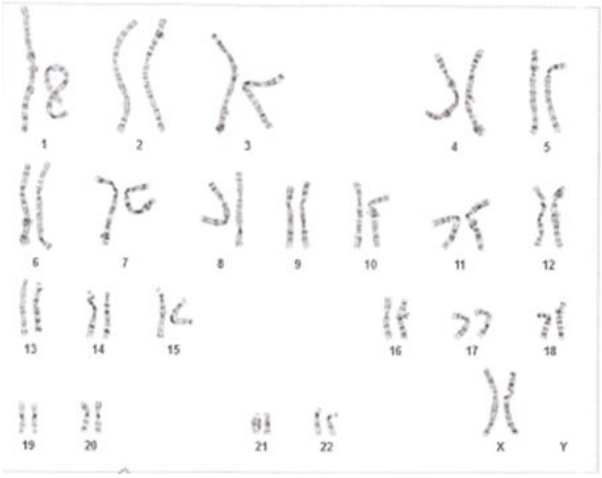

Figure 4. Karyotyping result of 46, XX.

3. Discussion

Primary amenorrhea is characterized by no menses by age 14 in the absence of development of secondary sexual characteristics or absence of menses by age 16 despite of the presence of normal growth and development of secondary sexual characteristics.[5]

When having primary amenorrhea, a comprehensive history and physical examination must be done. The presence or absence of secondary sexual characteristics such as breast development and the presence or absence of the uterus should be taken into consideration. Thus, the findings in physical examination can warn the clinician to possible causes and indicate which laboratory tests should be performed.

Our patient presented at adulthood with complaints of primary amenorrhea. Upon physical examination, the patient is phenotypically female with fully developed breasts at Tanner stage V, pubic hair at Tanner stage IV and presence of axillary hair. External genitalia were grossly female with a developed vaginal canal ending in a blind pouch. Internal examination and transvaginal ultrasound showed presence of infantile uterus and normal ovaries and absence of the cervix. For a patient with fully developed breasts and absent / infantile uterus, two conditions should be considered: androgen insensitivity syndrome and mullerian agenesis or Mayer-Rokitansky-Kuster-Hauser syndrome.

Androgen insensitivity syndrome (AIS) results from the inactivating mutation in the gene encrypting the intracellular androgen receptor (located on the X chromosome's long arm, Xq). End organ insensitivity to androgen actions that prevent normal masculinization of the internal and external genitalia during embryonic development occurs. Consequently, the characteristics of the external genitalia look like those of females due to (absent androgen action).The cervix and uterus are absent (due to normal Anti Mullerian Hormone action). The vagina however, is short and ends blindly since the lower two-thirds of the vagina is originated from the urogenital sinus. To differentiate AIS from MRKH syndrome, karyotyping is warranted. Patients with AIS have testes which produce both testosterone and AMH and a normal male karyotype of 46 XY while MRKH syndrome patients present with normal female karyotype. Our patient has 46 XX karyotyping result, thus, clinching the diagnosis for MRKH syndrome.

Mayer-Rokitansky-Kuster-Hauser syndrome consequences from failure of mullerian development. It is a multifactorial genetic syndrome, in which a female with a normal female karyotype is born with normal female secondary sex characteristics and functioning fallopian tubes and ovaries but with vaginal agenesis and uterine abnormalities that range from a rudimentary to an absent uterus. Mayer-Rokitansky-Kuster-Hauser syndrome is also related

with spinal, other skeletal, renal, and auditory anomalies. It is a rare disorder with an estimated incidence of approximately 1 per 4500 - 5000 females. However, it is the second most common cause of primary amenorrhea after gonadal dysgenesis.[4]

The cause of MRKH is unknown. Although usually sporadic, some causes of mullerian agenesis are either associated with translocations of chromosomes or those which occur in familial aggregates- suggesting a genetic basis for the disorder. Logically, mullerian agenesis is attributed to an activating mutation in the gene encoding anti mullerian hormone (AMH) or its receptor, causing excess AMH activity. However, no activating mutations have been identified in patients with mullerian agenesis.[4,5] The only known mutated MRKH-associated are found within the WNT4 gene and lead to an atypical form of MRKH syndrome linked with clinical and biochemical hyperandrogenism. In mice, the WNT4 gene regulates development of female reproductive tract and antagonizes testosterone production. The WNT4 mutation has been informed to be connected with failure of mullerian duct formation and virilization, including acne, in at least four 46 XX women. To date, four different WNT4 point mutations is being linked with women suffering from Mullerian duct regression and virilization. However, virilization is never seen in MRKH syndrome, and therefore, the loss-of-function mutations of Wnt4 are not likely to be the source of the syndrome in its original presentation. Given its very characteristics features and the advances given that by the work of the Biason-Lauber, further research is needed to clearly distinguish the syndrome with hyperandrogenism from classic Mayer Rokitansky Kuster Hauser syndrome.[4,6]

Müllerian agenesis typically shows up in a patient's late adolescence right after menarche is expected. Primary amenorrhea, inability to have intercourse, and dyspareunia are the most common presenting symptoms. Patients exhibit normal breast and pubic hair development with no visible vagina, and have no signs or symptoms of crytomenorrhea because the rudimentary uteri contain no functional endometrium. However, in approximately 10%, functional islands of endometrium may result in hematometra and symptoms of cyclic pain.[5] Our patient showed with primary amenorrhea. We assume that even in the presence of an infantile uterus, the endometrium of our patient is non-functional since there are no complaints of cyclic pelvic pain.

The two types of MRKH syndrome have been described. Type 1 is characterized by symmetrical, muscular, rudimentary uteri, and fallopian tubes are normal, and Type 2 by asymmetrical rudimentary uteri and absent or hypoplastic fallopian tubes. Most of patients with müllerian agenesis, the ovaries are entirely normal, but one or both also may be undescended, hypoplastic, or associated with an inguinal hernia. Urologic anomalies are relatively common (15–40%), particularly in Type 2 mullerian agenesis, and include unilateral renal agenesis, ectopic or horseshoe kidney, and duplication of the collecting system(s). Skeletal malformations involving the vertebrae, the ribs, or the pelvis are observed in 10–15% of patients; some of the more common abnormalities include hemivetebrae leading to scoliosis and the Klippel-Feil syndrome, characterized by a short neck, low hairline, limited range of motion, and sometimes pain and neurologic symptoms, all relating to one or more fused cervical vertebrae.[5] Reported elsewhere in literature are four cases of MRKH syndrome with hyperandrogenemia.[4] Our patient has MRKH syndrome Type 2 with presence of Tarlov cyst at S2 and hyperandrogenemia.

Our patient have an infantile uterus with normal ovaries and elevated serum testosterone. The elevated serum testosterone in our patient made us reconsider AIS. Thus, karyotyping was justified for definite diagnosis even though the MRI (the gold standard diagnostic for this case) revealed consideration to mullerian dysgenesis. Our patient had female karyotype result of 46 XX, thus clinching the diagnosis for MRKH syndrome.

There is lack of literature to explain the existence of elevated testosterone with no associated virilization

in our patient as well as in other MRKH patients.

The relationship of MRKH and clinical signs of hyperandrogenism needs more investigation. Further research is required to clarify the relationship between MRKH syndrome and the low frequency of acne despite the high frequency of hyperandrogenemia in MRKH women. The syndrome could be correlated to a genetic aberration, for example, a gene mutation that not only origins the MRKH phenotype but also partly prevents the skin from developing acne. This irregularity could cause androgen resistance similar to that in complete androgen insensitivity syndrome. There are no studies yet on the evaluation of hirsutism as a sign of hyperandrogenism among MRKH patients.[7]

The patient also presented with a Tarlov cyst. Tarlov cyst is a rare, often undetected disorder, characterized by isolated or multiple nerve-root cysts, usually arising in the sacral spine, near the dorsal root ganglion, among the perineurium and endoneurium. The cysts may cause lower back pain, sacralradiculopathy, dyspareunia and urinary incontinence. There is slight information in the literature on the association between Tarlov cysts and presentations.[8] These are abnormal sacs occupied with cerebrospinal fluid are isolated in the spinal and S1-S2 region of the fluid spinal cord and can cause a progressively painful radiculopathy. Tarlov cysts cane also be recognized as perineurial cysts. These are caused by increased CSF pressure filling the congenital cysts with one-way valves, resulting to inflammation due to trauma and disease. These cysts are often discovered incidentally during MRI or CT scans for other medical conditions. These are also observed with communicating subarachnoid cysts of the spinal meninges using magnetic resonance neurography. Current treatment options for tarlov cyst include aspiration of CSF, fibrin-glue therapy, removing partially or completely, wrapping of the cyst via laminectomy, among other surgical treatment approaches. Tarlov cyst can expand through time, especially if the sac has a check valve type opening.[8] The patient was advised to undergo treatments since she is having occasional low back pain. Due to financial problems, the patient chose intake of analgesics for temporary relief.

Although mullerian dysgenesis usually can be diagnosed by medical history and physical examination alone, additional evaluation is warranted to confirm the diagnosis and to identify any of the urologic (renal ultrasonography) and skeletal anomalies (spinal X-rays) associated with the disorder. Transabdominal, transvaginal, transperineal, or even transrectal ultrasound examination, due to its simplicity and non-invasiveness is the preferred initial diagnostic modality. However, identification of uterine remnants and Mullerian rudiments is often prevented by the acoustic window and peristalsis of the bowel loops. Magnetic resonance imaging (MRI) has greater sensitivity and specificity up to 100%.[9] We performed MRI in our patient to simultaneously evaluate for the presence of other associated anomalies, especially urinary tract and spinal. Magnetic resonance imaging is presently the gold standard in the assessment of Mullerian dysgenesis. Uterine anomalies are best revealed on sagittal planes, while vaginal anomalies are best visualized on transverse sections. Cardiac echograph, audiometry, intravenous pyelography, and skeletal studies may also be performed to detect associated congenital malformations. Laparoscopy usually is not necessary for diagnosis of mullerian agenesis.[1]

Management of MRKH syndrome patients should address functional, sexual, and psychological issues such as disclosure, functional vagina creation, and provision of genetic advice. Care needs to be individualized, flexible, and holistic. Management is dependent wholly on a multidisciplinary team with the inclusion of geneticists, endocrinologists, gynecologists, psychiatrists, surgeon and social workers in the team.

The desire of women with MRKH syndrome to attain a normal sexual life should be the only regulating factor for the timing of the appropriate therapeutic management. The functional vaginal

creation is the primary goal of treatment in women with Müllerian dysgenesis. This can be achieved with a variety of methods, when the time is appropriate. In general, the creation of neovagina should be postponed when the patient desires to be sexually active and is emotionally mature. In the large majority of cases, progressive vaginal dilation is an appropriate and effective first choice. In motivated patients, the technique is successful and can create a vagina which is functional within 3 to 6 months. While vaginal lengthening is necessary for penile penetration in some women with MRKH syndrome, others have a vaginal normal length and report satisfactory intercourse regardless of never having dilatation or surgery.[10,11] Our patient been sexually active for four years now with satisfactory sexual relations so there was no need for progressed vaginal dilatation. However, after the disclosure of the diagnosis, the patient reported periods of decreased sexual satisfaction with absence of orgasm and had periods of depression.[11]

Reassurance and support are important elements of the management of mullerian dysgenesis. MRKH woman should be counseled that although they are infertile, normal sexual function can be expected. The patient and her husband were educated on pelvic anatomy and advised modifications in sexual behavior so as to attain mutual sexual satisfaction. Emphasis was made about her part as a wife and a female capable of normal satisfactory sexual and interpersonal relationships. Supportive psychotherapy was also provided. Upon follow-up 5 months after diagnosis, the patient already reported having satisfactory sexual relations and showed acceptance of the diagnosis.

Surgery for MRKH syndrome patients is generally indicated only in those with symptoms relating to hematometra, endometriosis, or a hernia into the inguinal canal. Surgical intervention such as hysterectomy to remove uterine remnants is not indicated for our patient at present since she has no complaints of cyclic pelvic pain with no evidence of hematometra or endometriotic lesions on ultrasonography. The patient was instructed to observe presence of signs and symptoms of endometriosis or hernia into the inguinal canal. Once she experiences any of these signs and symptoms, she has to seek consult promptly for further evaluation and performance of surgery.

Historically, MRKH syndrome patients been told to be infertile with no chance for biological offspring due to lack of functional uterus. Even if our patient presented with an infantile uterus, we counseled her that spontaneous pregnancy is not possible since she has no signs of a functioning endometrium. However, we informed her that MRKH women may now have a chance for biological offspring following the introduction of gestational surrogacy. Genetic offspring can be achieved by assisted reproductive techniques (ART) through in vitro fertilization (IVF) wherein oocytes are retrieved from their own normal ovaries and the sperm of their chosen partner, with subsequent transfer of embryos to a gestational surrogate. As all MRKH syndrome patients lack a functional uterus, the current counseling of patients diagnosed with MRKH syndrome should include aspects of their reproductive potential. Presently, their reproductive function may be possible by undergoing uterine transplantation or IVF via a gestational surrogate.[12]

Response to gonadotrophin stimulation is comparable in MRKH syndrome women as those women with normal pelvic anatomy, since these patients are mostly, otherwise normal females with normal patterns of serum gonadotrophins and ovarian steroid cycle. We informed our patient of gestational surrogacy done abroad since gestational surrogacy is still not ethical in the Philippines as to the time of writing this paper.

Transplanting uterus is an experimental method that may permit fertility to carefully selected patients with MRKH in the absence of significant renal disease. It should be taken into account that the patient would potentially undergo three surgical procedures: uterus

transplantation, cesarean section, and uterus removal following completion of childbirth. The donor uterus can be harvested from a deceased or live donor and multiparous women with a live birth to miscarriage ratio of one (1) should be preferred.[10,13] If and when our patient is capable of uterus transplantation, a laparoscopic hysterectomy should be performed before uterus transplantation.

Prior to uterus transplantation, extensive consultation should be considered. This should include the risks of the surgical procedure, exposure to immunosupressive agents, and disclosure on the undetermined risk of genetic transmission of the disorder to their offsprings if genetic gestation is selected. For the first degree relatives, the risk of recurrence is around 1–5%.

The world's first transplanted uterus which gave birth to a baby boy was born at the University of Gothenburg in Sweden back in the year of 2014. Since then, the Swedish hospital has had a total of eight babies born to women who have established uterine transplants. In the United States, the first baby delivered in a mother who had received a uterus was born in December 4, 2017.[10,13]

Adoption is also an option for MRKH syndrome patients who, for one reason or another cannot avail of assisted reproductive techniques such as IVF with gestational surrogacy or uterine transplantation. Our patient is contemplating on adoption.

4. Conclusion

We present this case of a 21 year old, with a chief complaint of primary amenorrhea, with no visible cervix and with infantile or small uterus, presenting inactive endometrium based on the absence of cyclic pain. Incidental findings shows Tarlov cyst on the MRI that cause low back pain for the patient.

MRI is a gold standard for diagnosing an MRKH syndrome. The pathophysiology is still unknown. Finding MRKH syndrome with hyperandrogenism reinforces the likelihood that WNT4 is elaborate in mullerian development and ovarian function in humans.

There are no official protocol for MRKH syndrome with hyperandrogenemia management, but annual request for level testosterone is recommended or depends on the severity of the symptoms. Fertility options should be presented to the patient since MRKH syndrome patient has no functional uterus. The family of the patient should be counseled personally too, because there is a 1-5% chances for the relatives to have the anomalies. Good counseling is recommended.

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