Leiomyomas Arising from the Uterine Remnants of a Woman with Mayer Rokitansky Kuster Hauser Syndrome - A Case Report

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The Mayer Rokitansky Kuster Hauser Syndrome (MRKHS) is characterized by congenital absence of the uterus and the middle to upper thirds of the vagina. Women with this syndrome are genotypically female presenting with primary amenorrhea, female secondary sexual characteristics, normal ovarian function, absent or short blind vagina and the presence of uterine remnants or rudimentary uteri. The occurrence of leiomyoma in a patient with MRKHS arising from the fibromuscular tissues of uterine remnants is very rare. As the mullerian ducts have smooth muscles, the presence of a myoma is a possibility. This paper aims to explain the pathogenesis of leiomyoma arising from the uterine remnants in patients with MRKHS and to present a comprehensive review on the clinical presentation, diagnostic evaluation, and management of this condition. There is paucity of documented cases of leiomyoma associated with MRKHS reported in literature. This is a the first case reported locally.

Key words: Mayer Rokitansky Kuster Hauser syndrome, mullerian agenesis, primary amenorrhea, leiomyoma uteri

Introduction

The Mayer Rokitansky Kuster Hauser syndrome (MRKHS) is a form of aplasia of the mullerian ducts. In this anomaly, the fusion and further differentiation of the distal parts of the ductal system fail to occur during embryogenesis.[1,2] It is characterized by congenital absence of the uterus and middle and upper thirds of the vagina. It is also commonly referred to as mullerian aplasia or mullerian agenesis.[1,3]

The frequency of MRKHS is not yet entirely established but reported incidences vary from 1 in 4000 to 5000 female births.[2,3,4,5]

At the Philippine General Hospital, a seven year review covering 2002 to 2008 reported a total of eleven cases of Mayer Rokitansky Kuster Hauser syndrome. To date, this is the first reported case of MRKHS with the coexistence of a huge leiomyoma in our country.

The congenital absence of the uterus in a phenotypically female individual was first described by Mayer in 1829. This was followed by Rokitansky in 1838 to include agenesis of the vagina due to abnormal development of the mullerian ducts. In 1910, Küster recognized the urologic associations and skeletal deformities commonly seen in this condition. In 1961, Hauser distinguished this anomaly from testicular feminization. It was during this time that the syndrome was first given its current name, Mayer Rokitansky Kuster syndrome, eventually being extended to Mayer Rokitansky Kuster Hauser syndrome.[5,6]

The MRKHS is characterized by vaginal agenesis with rudimentary uterus, normal fallopian tubes and normally developed and functioning ovaries.[2] Ovarian function is intact and coordinated normally with pubarche and thelarche.[5] The karyotype is 46XX and the secondary sexual characteristics are typically female.[2,3]

Primary amenorrhea is the most common symptom complained of, motivating patients to seek consultation and thereby leading to the diagnosis and recognition of MRKHS. Although the uterus is not present, rudimentary uterine remnants or anlage are sometimes present. Variable development of endometrial tissue may be present,

resulting in cyptomenorrhea (concealed menstruation) and cyclic abdominal pain.[1,6,8]

This paper aimed not only to report the rare occurrence of a leiomyoma on the uterine remnants of a patient with MRKHS, but also to present a comprehensive review on the diagnosis, evaluation, presentation, etiopathogenesis and management of Mayer Rokitansky Kuster Hauser syndrome.

The Case

C.A. is a 42 year old, nulligravid from Cavite who was referred to our section for primary amenorrhea.

The past medical history was unremarkable. There is no similar history of amenorrhea and other menstrual problems or infertility in the patient's female siblings.

The patient was unemployed with no vices. Her first coitus was at 27 years of age with a monogamous sexual partner; their relationship lasted for 7 years prior to their separation. Presently, she is living with her common law husband of 8 years.

Patient never menstruated. Breast development occurred around 14 years old and pubarche followed a year later.

Two years prior to admission, patient finally consulted for primary amenorrhea concerned that the absence of menstruation would be harmful in her advancing age. No palpable cervix was appreciated on internal examination nor seen on speculum examination. Serums FSH, LH, prolactin, estradiol, free T4, and TSH were all within normal female limits. On KUB IVP, the kidneys, ureters and urinary bladder were all normal. On transvaginal ultrasound (figure 1), the uterus measured 9.8 cm x 7.6cm x 8 cm with the cervix measuring 1.9cm x 2.2cm x 1.5cm with note of multiple myoma uteri, 4 to 5 centimeters in widest diameter, intramural and intramural with subserous component. The endometrium was 0.3cm thin. Both ovaries were unremarkable. No hematometras or hematocolpos noted. The estrogen stimulation and progesterone challenge test done was negative. The initial impression then was: Primary amenorrhea with transverse vaginal septum and multiple myoma uteri with estrogen receptor deficient endometrium.

Since during this time, the patient had no complaints other than amenorrhea and had no more plans of getting pregnant, no intervention was deemed necessary. Patient was eventually lost to follow up.

One year later, patient started experiencing persistent hypogastric pain, sensation of pelvic heaviness radiating to the back and note of a palpable hypogastric mass. No consult was done. A month before admission, patient consulted again at the out patient department because of a palpable hypogastric mass.

On physical examination, Tanner Stage V was noted for both breasts development and pubic hair distribution. Findings centering on the abdomen revealed a palpable, firm, immovable mass occupying the pelvic cavity measuring 12cm x 10cm. The vagina was smooth with no visible cervix on speculum examination. On examination, there was a normal external genitalia, the vagina was smooth that ended in a blind pouch approximately 3cm in length. No palpable cervix was appreciated. Occupying the pelvic cavity was a nodular, firm, non- movable, asymmetrical mass approximately 12cm x 10cm x 12cm, slightly tender on deep palpation. The rectovaginal examination confirmed the findings of the internal examination.

The clinical impression at this time was: Primary amenorrhea probably secondary to Mayer Rokitansky Kuster Hauser Syndrome with a pelvic mass probably a myoma.

A transvaginal ultrasound (Figure 1) revealed a huge myoma measuring 12 cm x 8 cm x 9 cm and two uterine corpuses. The right hemiuterus measured 4.5 cm x 3.1 cm x 3.6cm without a distinct cervix and indistinct endometrial halo. The left hemiuterus measured 4.4cm x 3.7cm x 3.5cm with a hyperechoic endometrium measuring 0.3cm and no identifiable cervix. Both ovaries were visualized and were sonologically unremarkable.

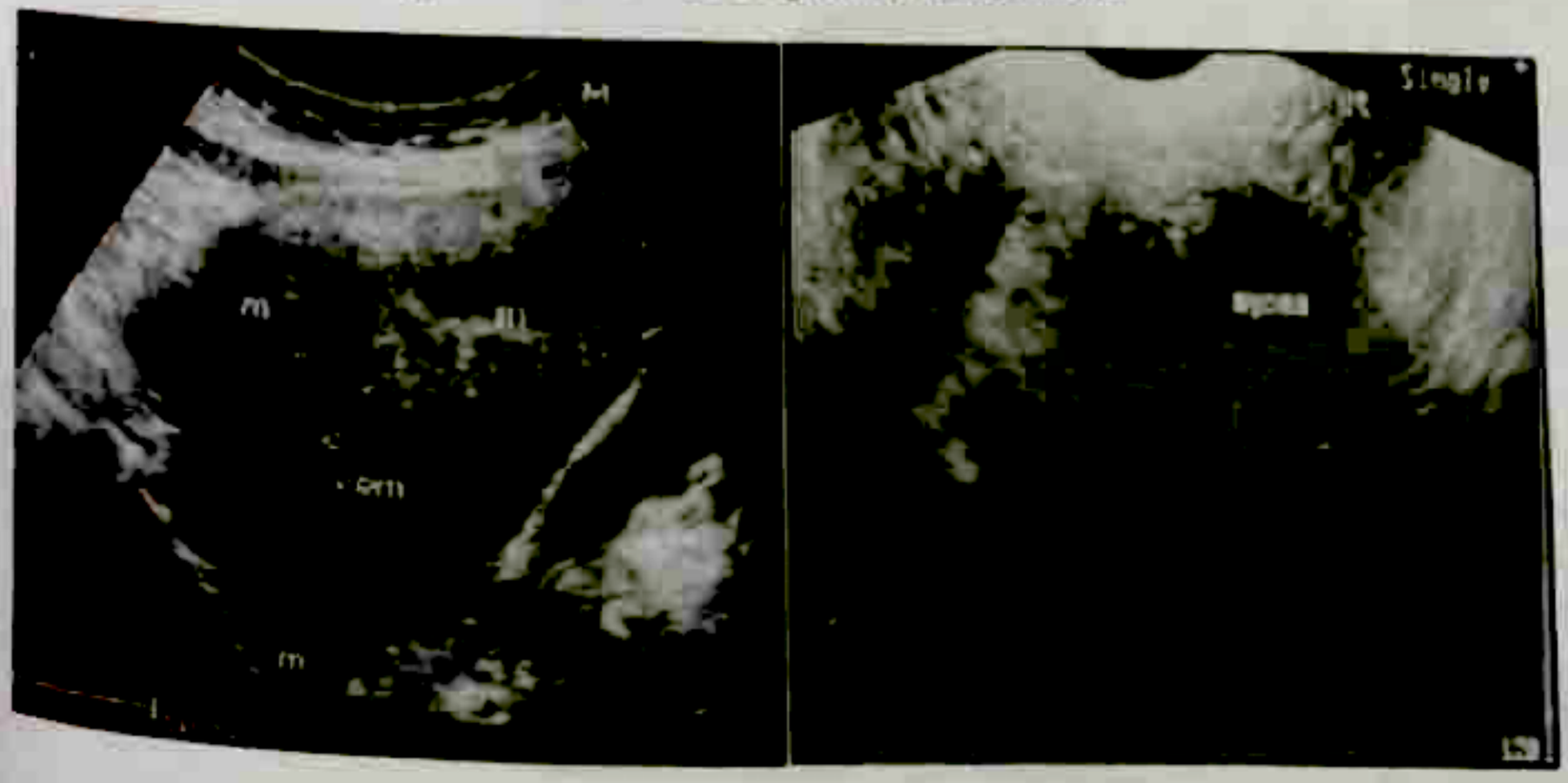

Figure 1. Transvaginal sonography of the pelvis. Left - scan done on initial consult showing the uterus with multiple myoma uteri and thin endometrium. Right - scan done on admission showing the huge leiomyoma between the two uterine corpuses.

Incongruity of the ultrasound findings in the presence of primary amenorrhea and a huge pelvic mass required further investigation.

The karyotyping done on the patient revealed a chromosomal make up of 46XX.

A magnetic resonance imaging (MRI) revealed a vagina which appears small and ends shortly at the level of S3 (Figure 2). No morphologic uterus and cervix were identified. A large mass with mixed abnormal signal intensities measuring 12cm x 10cm x 9.2cm was appreciated within the pelvis. Heterogenous enhancement was seen on contrast study.

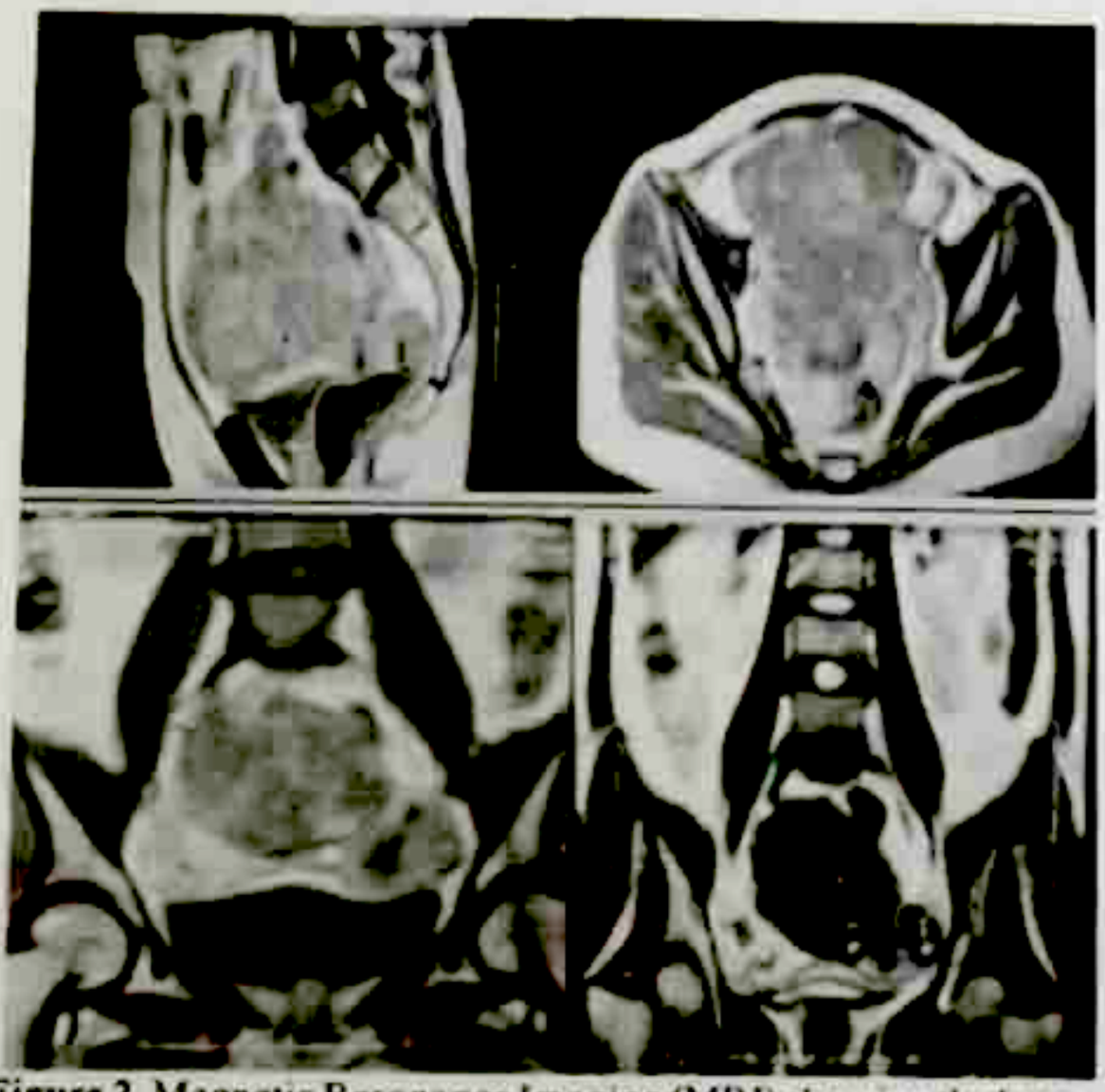

Figure 2. Magnetic Resonance Imaging (MRI) showing the large mass with mixed abnormal intensities and heterogenous enhancement on contrast study.

The patient underwent exploratory laparotomy and subsequent removal of the pelvic mass. Intra-operatively there was a well circumscribed nodular mass measuring 13cm x 11cm x 5cm (Figure 3). This was attached to the right uterine remnant measuring 2cm x 2.5cm x 1cm this was located near the right pelvic side wall. Cut section of which revealed no identifiable endometrial cavity. A left uterine remnant (Figure 5) was noted near the left pelvic sidewall measuring 3cm x 3cm x 2.5cm. Another well-circumscribed mass measuring 2.8cm x 2.5cm x 2.2cm, likewise with no identifiable endometrial cavity on cut section was noted (Figure 6). Cut sections of both well-circumscribed masses attached on the uterine remnants showed smooth cream white surfaces with whorled patterns without features of degeneration (Figures 4 & 6). Both remnants were attached laterally by a round ligaments and connected medially by fibrous band-like peritoneal fold (Figure 7). Both fallopian tubes and ovaries were grossly normal and were left behind. The rest of the abdominopelvic organs were unremarkable.

Figure 3. The right uterine remnant (R) with the huge leiomyoma.

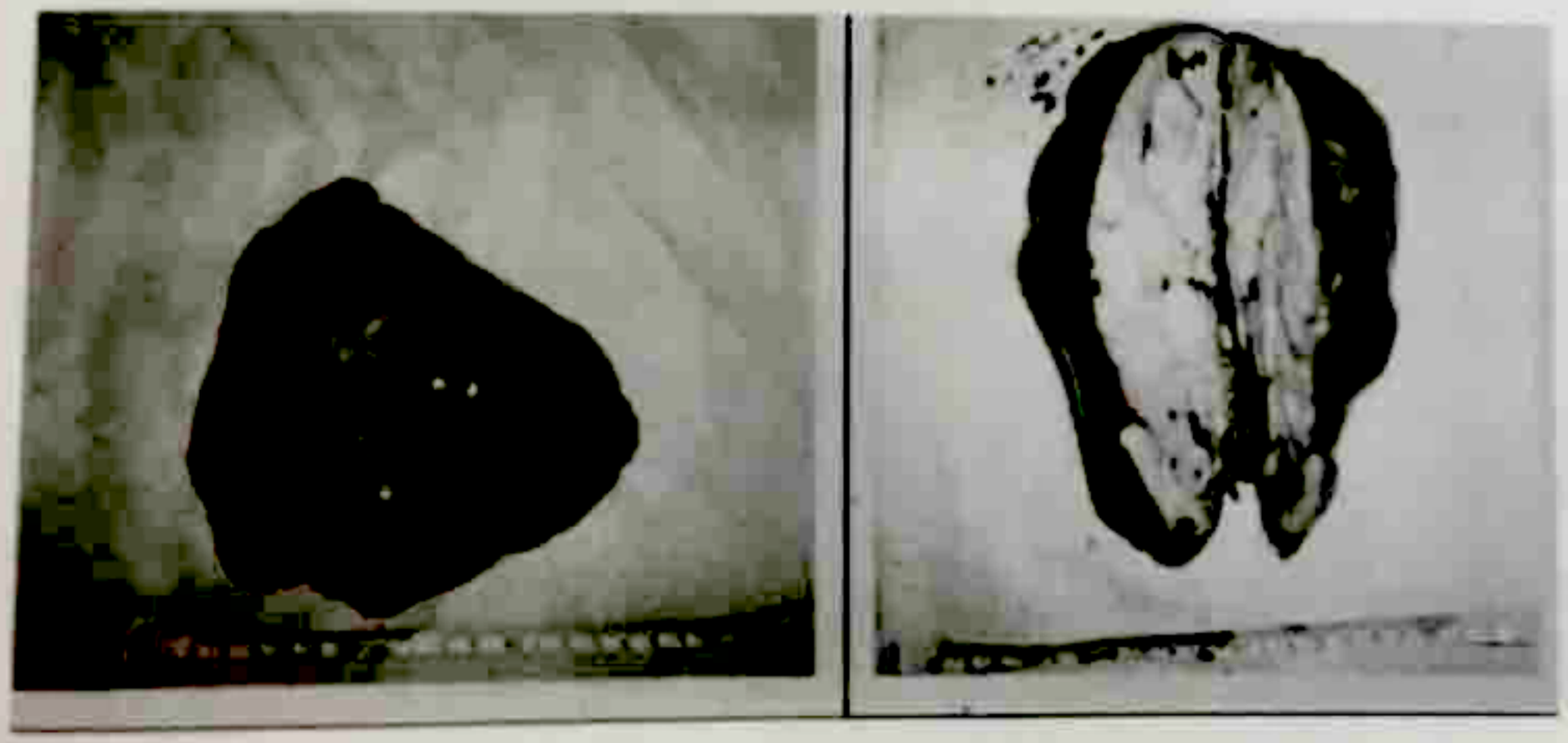

Figure 4. The huge well circumscribed leiomyoma taken from the right uterine remnant. Cut section of which showed smooth cream white surfaces with whorled patterns and no features of degeneration.

Figure 5. The right (R) and left (L) uterine remnants after the removal of the huge leiomyoma. Each remnant is attached to grossly normal fallopian tubes and medially connected by a fibrous peritoneal band.

Figure 7. The grossly normal fallopian tubes (F) and fibrous peritoneal band (B). Insert (Strubbe, 2003): Diagram showing the characteristics of Mayer Rokitansky Kuster Hauser syndrome: symmetric muscular buds or remnants (1), absence of normal uterus (2), rectum (3), and normal fallopian tubes and ovaries (4).

Figure 6. The left uterine remnant (L) with a small myoma (M) which on cut section showed smooth cream white surfaces with whorled patterns.

The histologic examination confirmed leiomyomas on both uterine remnants with basal endometrium.

Embryogenesis

Around week 5 of gestation, the male and female genital systems are indistinguishable in appearance, constituting two sets of paired ducts: the Mullerian and Wolffian ducts. In a genotypic female embryo, the Mullerian ducts persist while the Wolffian ducts regress. Eventually, the Mullerian ducts fuse in the midline and the uterus is formed at about the 10th week, with the fusion beginning in the middle of the uterus and proceeding cephalad and caudad.[1,7] The unfused cranial parts of the ducts differentiate into fallopian tubes. The distal segments induced by or derived from the adjacent mesonephric ducts, progress caudomedially and join each other before meeting the posterior aspect of the pelvic urethra at the level of the sinusal tubercle. These distal segments of the uterovaginal canal give rise to the uterus and upper four-fifths of the vagina.[7]

In MRKHS, the pathophysiology is a non-fusion of the mullerian ducts in the fifth to the seventh week of embryological development. This explains the fact that in a classic case of MRKHS, the fallopian tubes with very small parts of the cornu uteri extend only as far as the connection with the round ligaments of the uterus. Because the fallopian tubes are derived from a different cellular origin, they are rarely involved in mullerian duct anomalies.[9]

The ovaries arise from the mesenchyme and epithelium of the gonadal ridge and are not influenced by the formation of the mesonephric or paramesonephric ducts. Hence, ovarian development is a separate process from the formation of the uterovaginal canal and is not usually associated with mullerian duct anomalies.[7]

In the third to fifth month of gestation, the vaginal canal that becomes the outer one-third of the vagina fuses with the sinovaginal bulb of the Mullerian ducts above to form a horizontal vaginal plate. The cannalization of this should result in the inner two-third of the vaginal canal, but fails to occur in MRKHS.[1,9]

The urinary and genital systems both arise from a common ridge of mesoderm arising along the dorsal body wall, and rely on normal development of the mesonephric system. The ureters, renal calices, and collecting tubules, on the other hand, are formed from the ureteral bud, which arises from the mesonephric ducts, which also induce formation of the kidneys.[1,7] This explains why abnormal differentiation of the mesonephric and paramesonephric ducts may also be associated with anomalies of the kidneys.

Etiology

Although the pathogenesis of mullerian agenesis is now well described, its etiology remains unknown. The MRKHS was initially considered to be of random occurrence, suggesting the involvement of non-genetic or environmental factors such as gestational diabetes or thalidomide-like teratogens. However, recent studies analyzing available pregnancy histories failed to identify any association with drug use, illness, or exposure to known teratogens.[3,4]

The majority of reported cases of MRKHS are sporadic, but familial cases have been reported in literature.[4] The possibility of dominant hereditary transmission has been theorized due to its familial occurrence.[4] However according to a recent study (2008) by Wottgen, dominant inheritance does not play a role in the etiology as no further cases of this condition occurred among any of the siblings.[2]

Several hypotheses have been postulated for the underlying mechanism in the etiology of mullerian agenesis. The first is an activating mutation of either the gene for the anti-mullerian hormone or the gene for the anti-mullerian hormone receptor. This defect results in the inappropriate production of anti-mullerian hormone or the receptor which acts as if it was bound to the hormone. A genetic female fetus exposed to anti-mullerian hormone in-utero during embryogenesis at a time when the mullerian structures are sensitive to anti-mullerian hormone action, might develop regression of the mullerian ducts.[4] However, a recent molecular investigation did not identify any deletions or polymorphisms in the promoter region of the anti-mullerian hormone. Measurements of mullerian inhibiting substance (MIS) in affected patients did not demonstrate any increased serum concentrations. Over expression of MIS was therefore not present.[5]

In recent molecular studies, genes with a broad spectrum of activity during early development have also been suggested as candidates for the etiology of MRKHS. These major developmental genes regulate cell and tissue growth and differentiation during embryogenesis. More specifically, they appear to be essential for the initial differentiation of the mullerian ducts. Expression and/or function defects of one or several of these genes may play a role in the occurrence of MRKHS.[4,11]

Presentation

The main characteristics of the MRKHS are: vaginal agenesis, with a shallow dimple at the introital area representing a blind vagina; absent uterus or an extremely rudimentary one; normally developed fallopian tubes; normal and functional ovaries; aprropriately developed secondary sexual characteristics; and in some, association with anomalies of the urinary and skeletal system, middle defects, and hearing loss.[1,12]

Approximately 6 to 10 percent of these patients complain of chronic pelvic pain. Endometrial tissue or even variable development of the uterus with hematometra may be present, resulting in cyclic abdominal pain.[1,13]

Fedele, et al. recently described the anatomic variety of findings observed in 106 patients with MRKHS. In majority of the cases, the vaginas were no more than shallow invaginations of the vestibular mucosa at the normal sites of the vaginal orifices. In all cases, the uterus were absent. The uterine remnants were bilateral in the majority of the cases. The biggest observed was 4.5 cm. The smaller mullerian remnants were described as club-shaped, whereas the larger ones appeared uterus-like. The round and uteroovarian ligaments as well as the tubes were always present. The smaller uterine remnants were always non-cavitated whereas in 25.9 percent of cases, the larger remnants were cavitated and contained endometrial mucosa. A fibromuscular streak located at the vesicorectal fold was observed in a few, whereas in most cases, a simple peritoneal folds were found. The connecting strand is

generally thought to represent the anlage of a rudimentary cervix. The ovaries in these studied cases were either absent unilaterally or bilaterally present or have marked hypoplasia. In some cases, the ovaries were extrapelvic in location.[14]

The index patient fits the typical presentation of a patient with the MRKHS. She presented with primary amenorrhea. On physical examination, the breast development and pubic hair distribution were Tanner Stage V, the vagina was shallow at 3cm in length and there was no palpable cervix. The presence or the absence of the corpus cannot be assessed due to the existence of a huge pelvic mass. Intra-operatively, the two laterally attached solid, muscular, rudimentary uterine remnants connected by midline fibrous bands were in place of the uterus. These remnants were attached to the pelvic side walls by the presence of round ligaments on each side. Cut sections of the uterine remnants showed no identifiable endometrial cavities. Each remnant was attached to grossly normal fallopian tubes and ovaries.

Diagnostic Evaluation

In most instances, a gynecologic physical examination is enough to narrow down the differentials between MKRHS and Androgen Insensitivity Syndrome (AIS).[15,16] Karyotyping will readily determine which of the two conditions we are actually dealing with. An individual with MKRHS will have a chromosomal makeup of 46XX while a patient with AIS will have 46XY.[17] In addition, the hormone profile in MRKHS will typically be that of a woman. The follicle stimulating hormone (FSH), luteinizing hormone (LH) and 17ß-estradiol are within normal limits and provide evidence of normal and functional ovaries. The plasma level of testosterone, delta-4-androstenedione, 17-hydroxyprogesterone and dehydroepiandrosterone are within normal female limits for MRKHS and in the normal male range for AIS.[3]

In the evaluation of primary amenorrhea, a progesterone challenge test is of great value in the determination of the relative estrogen status of the patient and will test the integrity of the outflow tract.[18] Any uterine bleeding after the progesterone challenge test indicates adequate estrogen production, a responsive endometrium, and a patent outflow tract. If the progesterone challenge test is negative, one may proceed with performing an estrogen stimulation-progesterone challenge test.[18] If bleeding occurs in the endometrial cavity after estrogen progestogen stimulation, then the amenorrhea after the progesterone challenge test is due to hyperestrogenism. When there is no endometrial bleeding but does not show in the vagina, this signifies non-patency of the outflow tract, a condition known as cryptomenorrhea and demonstrated sonologically as hematocolpos or hematometras. If endometrial bleeding is absent after the progesterone challenge test and the estrogen-progesterone challenge test than the patient is likely to have an estrogen insensitivity of the endometrium, especially in women with adequate female sexual maturation.[17,18]

This was what was initially thought to be what the patient had, having a "uterus" in her initial ultrasound findings, throwing the diagnosis off course.

In evaluating patients with suspected MRKHS, ultrasonography is an excellent imaging modality. The first investigation should be pelvic ultrasonography because of its simplicity and low cost. It is also readily accessible. It easily detects absence of the uterine structure between the bladder and the rectum.[7,10]

If the ultrasonographic findings are indeterminate or inconclusive, an MRI should be performed as the information is much more precise. MRI is the mainstay of imaging evaluation of MRKHS, not only to confirm clinically diagnosed Mullerian anomalies of uterus but also to assess the degree of vaginal dysgenesis and presence of associated anomalies which have an impact on the planning of treatment.[8] An MRI, owing to its multiplanar capability and best soft tissue contrast, gives good images of superficial and deep planes. The disadvantages of an MRI include cost and discomfort, especially because the procedure lasts long and requires immobility and magnetic insulation.[7,10]

There is no role for MRI in discriminating between the typical and atypical forms of MRKHS. It may be useful for showing small amounts of endometrial tissue in patients who have cyclic abdominal pain.[19] The normal ovaries are well demonstrated and normal follicles can be identified. Visualization of normal ovaries is one of the major factors in the diagnosis of MRKHS.[8]

Since renal and skeletal abnormalities may often co-exist with this condition, it is necessary to perform at least renal sonography or pyelography and spine radiography.[10,19] If there is a suspicion of hearing impairment and/or a cardiac anomaly, complementary audiogram and/or heart echocardiography must also be carried out.[3]

Association with Leiomyomas

Uterine myomas are the most common solid tumors in the female pelvic cavity. Myomas arise from genetic alteration in a single myometrial cell and hence often are described as monoclonal.[17]

A limited number of documented cases of myoma uteri associated with MRKHS have been reported in literature. The association of MRKHS with a myoma was

literature. The association of MRKHS with a myoma was first reported in 1977 by Beecham and Skiendzielewski.[11]

Uterine remnants in MRKHS patients consist of fibromuscular tissue. Since the ovaries in these cases are hormonally functional, following the same pathogenetic mechanisms as in normal uteri, tumors like leiomyoma can originate from these remnants.[11]

Cytogenetic abnormalities in the form of spontaneous chromosomal rearrangements are known to occur in uterine leiomyomas. These same chromosomal arrangements may be responsible for the initiation and progressive growth of the leiomyomas in MRKHS. Myometrial tissues developing into leiomyomas are found to have higher concentration of estrogen receptors compared to normal myometrium. Apparently, from this condition, the uterine remnants in MRKHS are not exempt.[20]

Management

The management of vaginal agenesis in MRKHS should be individualized. The aim is for a satisfactory sexual activity with a good anatomical and functional vagina.[10,21,22] Treatment may either be surgical or non-surgical. This is usually delayed until the patient is ready to start sexual activity.[21,22,23,24]

Our patient had no need for a vaginoplasty. She was married 7 years to another man prior to her present 8-year relationship with her common law husband and had no problems having sexual intercourse in those 15 years.

There is no recommendation to remove the uterine remnants when the patient is asymptomatic. When resection of a uterine remnant is indicated, a laparotomy is preferred especially if the patient complains of pelvic pain or develops a huge pelvic mass, as in this case, to allow exploration and adequate field of surgery. Excision of a uterine remnant by laparoscopy may be considered if no other pathology is suspected and the vestiges are small enough to be manageable through this approach.[9]

When leiomyomas are present on uterine remnants, the removal of these masses with the adjacent uterine remnants are indicated specially when the patient is symptomatic. In this case, the large myoma on the right uterine remnant was causing pressure symptoms which necessitated the exploration. The prophylactic removal of the opposite uterine remnant should be performed at the same time because another myoma may arise similarly from this. Although rare, the uterine remnants may also contain functioning endometrium that may lead to hematometra and cylic pelvic pain necessitating another surgical intervention.[12,20] In our case, the left uterine remnant was removed because it had a small myoma.

During exploration, the entire pelvis was inspected. The ovaries, fallopian tubes, uterine remnants, bladder and ureters were identified. Palpation of abdomino-pelvic organs was done. Myomectomy was then accomplished by triple clamping, cutting and suture ligation at the base of the huge myoma attached to the right uterine remnant. Excision of the right uterine remnant was then undertaken as follows: the round ligament was grasped with Kelly clamps, cut and suture-ligated. Then triple clamping at the uterine remnant-tubal junction, followed by cutting and tying beneath the most lateral clamp and suture ligation beneath the middle clamp. A sequence of Kelly clamps were then placed along the posterior peritoneal attachment of the remnant followed by cutting and suture ligation. The same technique was employed for excision of the left uterine remnant.

The decision to leave the ovaries behind is understandable enough, but the wisdom in retaining the "useless" fallopian tubes may not be that apparent. During gynecologic surgery, it has been a debate whether salpingectomy affects ovarian function. One of the concerns against salpingectomy is the possibility of impairing the ovarian perfusion after the procedure. The most important blood supply to the fallopian tube is the medial tubal artery which originates at the same point as the median ovarian artery.[17] If the salpingectomy is performed close to the tubes, it may inadvertently disrupt the normal blood flow to the ovary which might eventually result to premature ovarian failure. We intentionally left behind the grossly normal fallopian tubes of this patient for the same reason. After all, the risk of a primary malignant pathology arising from the oviducts is only 0.5% to 1%, making the choice to save the fallopian tubes an easy one.[17]

Psychological Considerations

Just as much attention must be given to the psychosocial issues as well as the anatomical abnormalities in these cases. Patients with MRKHS might suffer from severe distortions of body image, anxiety, depression, interpersonal sensitivity and face a lot of psychological distress at the time of diagnosis.[9,26] These may be avoided by early appropriate guidance and reassurance.[9,27] It is recommended that the patient and her family attend counseling throughout treatment. It is important to stress to the young woman and her family that she has normal ovarian function, normal production of sex steroids, that a functional vagina can be created, and that fertility is possible with assisted reproductive technologies and a gestational carrier.[18,28,29] Women afflicted with MRKHS in the United States have formed support groups and

condition and provide networking resources for women living with MRKHS.[18] Fortunately, sexual function, fertility, and body image were not considered areas of concern by our patient.

Fertility Issue

What if our patient was younger and highly desirous of pregnancy? Since ovarian function is completely normal, it is possible to offer motherhood through a combination of in-vitro fertilization (IVF) and surrogacy.[28] The introduction of ovulation induction with oocyte retrieval for in-vitro fertilization using gestational carriers enable these patients to fulfill their reproductive aspirations of having their biological children.[29]

The study of Beski, et al. in 2000, on women with the MRKHS proved that surrogacy is a viable treatment option for these patients. In this study, 6 patients with MRKHS underwent ovarian stimulation cycles. The treatment cycles resulted in 6 clinical pregnancies (42.9% pregnancy rate per embryo transfer and 54.5% per ovarian stimulation cycle) and 3 live births (21.4% per embryo transfer, 27.3% per ovarian stimulation cycle and 50% per patient) making the take home baby rate 50% per patient.[29] In an earlier study by Wood, et al. a live birth rate of 45.5% was achieved per patient with a fertilization rate of 49% per oocyte. Hence, these patients should be well-informed and supported to be able to have families using their own gametes.[30]

Conclusion

When our patient consulted, she was already at the mature age of 40 years old. She understood that she was already beyond the age to concern herself about not having menstruation, but was concerned with its implications in her advancing age. A palpable hypogastric mass accompanied by persistent hypogastic pain led to her admission, eventual diagnosis and surgical treatment.

She was resigned to the fact that she could not bear children and did not aspire anymore for this. She was happily living with her present partner for 8 years and was thankful that finally she had the answers to the questions she has been secretly wondering about for the past decades.

The importance of understanding the embryology and the physiology of the female reproductive anatomy cannot be overemphasized when managing cases of Mullerian anomalies. A systematic work-up and the individualization in the planning of its treatment, as demonstrated in this instance, should always be kept in mind.

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