Adenomyosis in Mayer-Rokitansky-Kuster-Hauser Syndrome*

By Laurice Gizelle C. Ramos, MD, Maria Lilia T. Reyes, MD, FPOGS and Debby F. Pacquing-Songco, MD, FPOGS, FPSRM
Department of Obstetrics and Gynecology, University of the East – Ramon Magsaysay Memorial Medical Center

ABSTRACT

Mayer-Rokitansky-Kuster-Hauser syndrome, the second most common cause of primary amenorrhea, is a congenital anomaly caused by defective Mullerian duct development. It is the absence of uterus, cervix and upper two thirds of the vagina that results in primary amenorrhea. This is a case of a 42-year-old, nulligravid with primary amenorrhea complaining of acute abdominal pain. She has no co-morbidities or previous surgeries. Examination revealed an absent cervix and a left adnexal mass. Ultrasonography revealed an atrophic uterus with no endometrial stripe and cervix, with possible ovarian tumor versus myoma. Impression was mullerian agenesis with pelvoabdominal mass in torsion. She then underwent total abdominal hysterectomy with bilateral salpingectomy and adhesiolysis. Intraoperatively, there were two hemiuteri connected by a fibromuscular stalk. Left hemiuterus was dextrorotated, adherent to the sigmoid mesentery and peritoneum. Histopathology confirmed absence of endometrial cavity but with adenomyosis in bilateral uterine buds. Chromosomal analysis confirmed 46, XX karyotype.

Keywords: Adenomyosis; Primary Amenorrhea; Mullerian Agenesis

INTRODUCTION

Mayer - Rokitansky - Kuster - Hauser (MRKH) Syndrome results from defective embryologic development of the mullerian duct. The condition ranks as the second most common cause of primary amenorrhea affecting one in 4500 to 5000 newborn females.[1,2] This type of Mullerian anomaly belongs to Class I of the classification of Mullerian Anomalies by the American Fertility Society and Class 5 based on the European Society of Human Reproduction and Embryology and European Society of Gynaecological Endoscopy (ESHRE/ESGE).[1] It is characterized by congenital absence or hypoplasia of the uterus, cervix and upper two-thirds of the vagina in a woman with normal secondary sexual characteristics and a 46, XX karyotype.[1-9] Its etiology is still unknown and is detected upon evaluation of affected individuals presenting with primary amenorrhea.[2]

Adenomyosis is a benign disorder denoting heterotopic growth of endometrial glands and stroma into the myometrium.[3] It is characterized by diffuse uterine enlargement, although some present with focal nodular lesions. Clinically, it presents with cyclic pelvic pain, menorrhagia and dysmenorrhea. Although ultrasound can clinch the diagnosis of adenomyosis, the definitive diagnosis can only be made by histology report. It is generally estimated that adenomyosis is present in 20 to 35 percent of women.[3]

The incidence of adenomyosis developing in the uterine buds of a patient with MRKH is rare with only a few reported cases.[4,5,7,9] The discussion of this case aims to explain that although rare, adenomyosis can develop in the uterine remnants in patients with Mayer-Rokitansky-Kuster-Hauser syndrome, even in the absence of an endometrial cavity.

CASE REPORT

The patient is a 42-year-old, nulligravid, Filipino, married, with primary amenorrhea and primary infertility presenting with progressive abdominal pain of three days duration. The pain was described as dull, non-radiating, localized to left lower quadrant area, severe in intensity and was unrelieved by intake of analgesics and antispasmodics. The patient also reported cyclical infraumbilical abdominal pain during the last five years. The patient had previous consult with a gynecologist at the age of 18 for her amenorrhea, diagnostic tests were requested but patient failed to comply. The patient has no other known medical illness or previous surgeries. None of the family members are known to have any forms of congenital anomaly. The patient has been married for ten years and has one sexual partner. She experiences dyspareunia and has no post-

*Finalist , Philippine Obstetrical and Gynecological Society (Foundation), Inc. (POGS) Interesting Case Paper Contest, September 12, 2019, 3rd Floor Assembly Hall, POGS Building, Malakas Street, Diliman, Quezon City

coital bleeding. The patient claims that quality of sexual life as a couple is adequate. On physical examination, she is 154 centimeters in height and 56 kilograms in weight with a BMI of 23.61 kg/m^2. Breasts and pubic hair were Tanner Stage 5. There were no note of anosmia, webbed neck, and thyroid enlargement. Extremities were grossly normal.

On abdominal examination, there was direct tenderness on the left lower quadrant, with no ascites and abdominal enlargement. Speculum examination revealed a smooth vaginal mucosa ending in a blind pouch. On internal examination, the vaginal canal was approximately two centimeters. No cervix was palpated. At the left adnexal area is a smooth and doughy mass which measured around 5 x 5 centimeters. On rectovaginal examination, there was good sphincter tone, smooth rectal mucosa, pliable parametria and no fullness in the cul-de-sac.

Transabdominal ultrasonography showed two pelvoabdominal masses to consider solid ovarian tumor versus pedunculated myoma uteri, cannot rule out torsion. The masses were described as well-circumscribed and heterogenous, measuring (1) 5.09 x 5.23 x 4.98 centimeters (volume: 69.41 ml) and (2) 5.39 x 4.78 x 4.47 centimeters (vol: 60.30 ml). Separate from the masses was an atrophic uterus measuring 1.99 x 2.46 x 1.51 centimeters. Neither endometrial stripe nor cervix was visualized (Figure 1). Both kidneys were normal in size with regular marginal outline and homogenous echopattern. Negative for hydronephrosis. CA-125 was elevated at 496 u/ml. Impression at that time was Mayer-Rokitansky-Kuster-Hauser (MRKH) with pelvoabdominal mass, in beginning torsion. The progression of abdominal pain did not allow further work- up, and plan was to proceed with exploratory laparotomy and total abdominal hysterectomy with bilateral salpingectomy and adhesiolysis.

Intraoperatively, two masses were noted, mass 1 measured 7 x 3 x 2.5 centimeters and mass 2 measured 7 x 7 x 5 centimeters. These were believed to be the hemiuteri connected by a fibromuscular stalk. The left hemiuterus was noted to be dextrorotated and adherent to portion of sigmoid mesentery and peritoneum on left pelvic sidewall, hence adhesiolysis was done. The round ligament on each side was cut and suture ligated. Ureters on both sides were identified. Both ovaries were grossly normal. Uteroovarian ligament on both sides were cut leaving behind the ovaries. Uterine vessels clamped and suture ligated on both hemiuteri. Bladder was separated from the fibromuscular tissue by careful blunt dissection. Uterine vessels and the uterine isthmus with each pedicle were cut and suture ligated until the end level of the fibromuscular tissue connection. The pseudostump was closed using an absorbable suture in a continuous interlocking suturing technique.

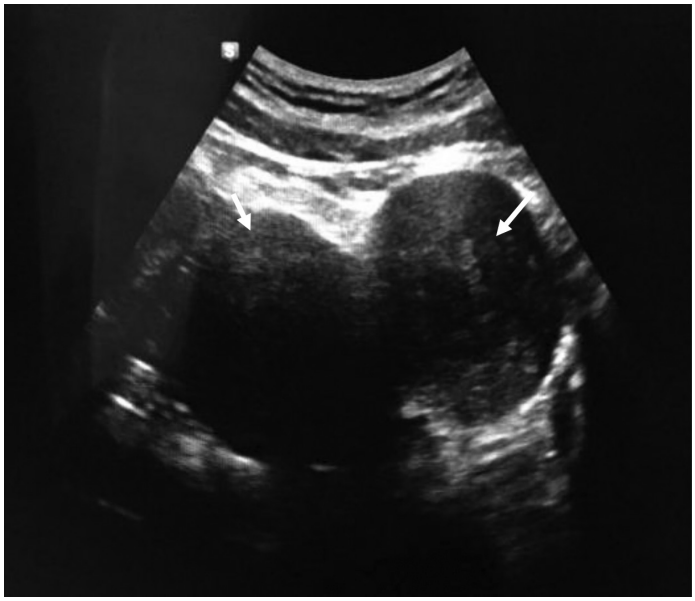

Figure 1. Transabdominal ultrasound shows pelvoabdominal masses to consider solid ovarian tumor versus pedunculated myoma uteri, cannot rule out torsion. The masses were described as well-circumscribed and heterogenous separate from an atrophic uterus measuring (1) 5.09 x 523 x 4.98 cm (vol: 69.41 ml and (2) 5.39 x 4.78 x 4.47 cm (vol: 60.30 ml). No endometrial stripe and cervix visualized.

The fibromuscular stalk connecting the uterine buds terminates in a blind end. The entire stalk measured 3 x 2 x 2 centimeters this was probably the atrophic uterus noted in the ultrasound. On cut sections, there were several dark red to dark brown nodules seen in the hypertrophic myometrium with no endometrial stripe identified. The connection between the right and left uterine buds showed no patent lumen or lower uterine segment. Bilateral fallopian tubes were normal, each connected to its uterine bud with a patent canal. (Figures 2 and 3).

Histologic examination (Figures 4a and 4b) showed an intact myometrium and parametrium in the right and left uterine buds with no identifiable endometrial canal and no distinct endometrial lining. There were only islands of irregularly oriented endometrial glands with the corresponding scanty endometrial stroma with interstitial edema and congestion within the myometrium of both uterine buds. Gross and histopathologic report were consistent with Mullerian agenesis and adenomyosis both in the right and left uterine buds. No findings of pathologic significance on bilateral fallopian tubes. No evidence of malignancy.

Post-operative course was unremarkable. The patient and her husband were counselled regarding her condition and reproductive potential. Chromosome analysis revealed 46, XX, normal female karyotype in all cells examined, with no evidence of a chromosomal abnormality.

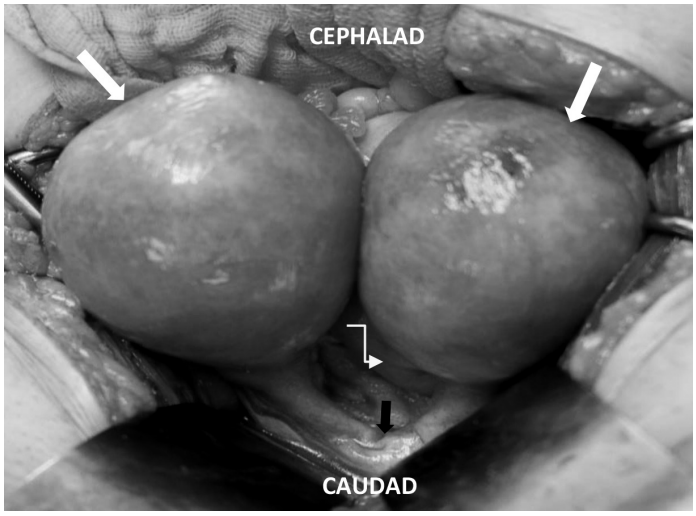

Figure 2. Intraoperative pictures showing two hemiuteri (white arrows). Right and left hemiuterus measures 7 x 3 x 2.5 cm and 7 x 7 x 5 cm, respectively. The uterine buds were attached to a fibromuscular stalk (black arrow). The entire stalk measures 3 x 2 x 2 cm. Adhesion of left hemiuteri to the distal descending colon is also shown (yellow elbow arrow).

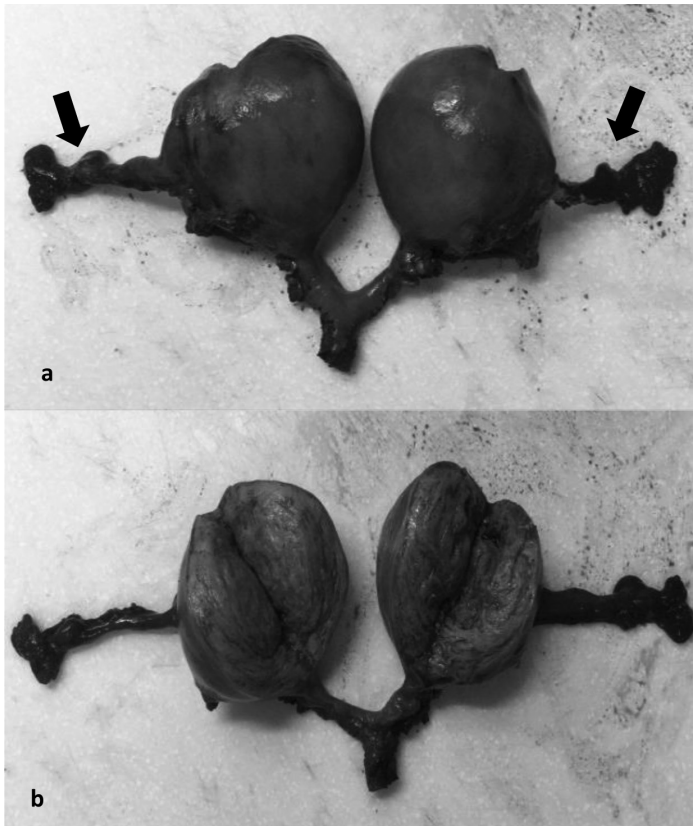

Figure 3. Grossly, (a) uterine buds are incompletely fused connected by a fibromuscular stalk that has no cervical canal and terminates with a blind end cervical stump. Bilateral fallopian tubes are normal. The right fallopian tube measures 10 x 1 x 0.2 cm and the left fallopian tube measures 11 x 0.8 x 0.2 cms. (b) On cut section, the uterine buds. have several dark red to dark brown nodules seen in the hypertrophic myometrium with no endometrial stripe identified. Bilateral fallopian tubes were normal.

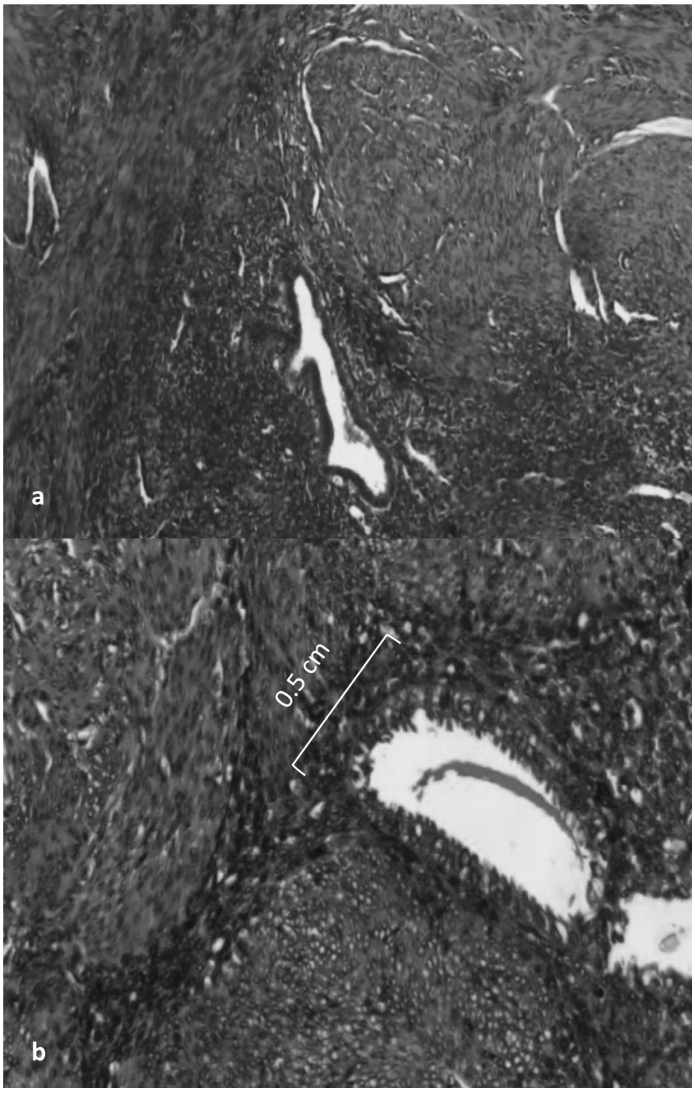

Figure 4. Histologically, on low power magnification (a) shows proliferation of spindle shaped smooth muscles on both uterine buds. There was no identifiable endometrial canal and no distinct endometrial lining. (b) On high power magnification, there were irregularly oriented endometrial glands with the corresponding scanty endometrial stroma with interstitial edema and congestion seen as nodules within the myometrium with the largest measuring 0.5 cm in greatest dimension (white bracket).

CASE DISCUSSION

Mayer-Rokitansky-Kuster-Hauser (MRKH) is a syndrome originating from the arrest in the development of the Mullerian ducts. According to ESHRE/ESGE, it belongs to the most severe uterine malformation category characterized by absence of the uterus, cervix and upper vagina.[1] in a genotypically and phenotypically nomal females. The condition may also be associated with renal, skeletal, hearing and cardiac problems. There is still no clear etiopathogenesis of the condition, but both sporadic and familial cases have been reported.[1,2,5] There are two

subtypes of MRKH: MRKH Type I in which only the upper vagina, cervix and the uterus are affected, which is the case of the patient reported; and MRKH Type II or Mullerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia (MURCS).[1,2,5] Patients with MRKH primarily seek consult for primary amenorrhea. Differential diagnosis for patients presenting with primary amenorrhea include structural abnormalities such as outflow tract obstruction or developmental receptor defects like in androgen insensitivity syndrome (AIS). Physical examination serves as the initial evaluation to determine etiology of primary amenorrhea. In patients with mullerian agenesis, secondary sexual characteristics are appropriate for age but pelvic examination will reveal a blind vaginal pouch like in the case of the patient. On the other hand, outflow tract obstruction like imperforate hymen will appear as a bluish-colored bulging membrane without the typical hymenal fringe and transverse vaginal septum usually will have normal hymen with more proximal obstruction.[2] Another condition that may present with primary amenorrhea, shortened vagina, and bilateral masses mimicking ovaries is androgen insensitivity syndrome (AIS). They may have typical thelarche due to peripheral aromatization of testosterone to estrogen. These patients however have a 46 XY karyotype, confirming its diagnosis. The index patient's karyotype was evidently 46 XX, hence affirming MRKH. Among the reported cases on mullerian duct anomalies, the remnants are usually examined and excised either through laparoscopic[4] or abdominal approach as Total Abdominal Hysterectomy.[9]

Patients with MRKH present with primary amenorrhea and primary infertility but only a few have been reported to have concomitant adenomyosis, especially in the case of no functional endometrium.[4,7,9,10] This case report discusses pathogenesis of adenomyosis in patients in the absence of an endometrial cavity.

Adenomyosis is the presence of endometrial tissue within the myometrium. This presents as cyclic pelvic pain and menorrhagia in affected patients with functioning endometrium. Among the few reported cases of adenomyosis in MRKH patients, the first reported case was by Enatsu, et al in their study in 2000.[4,7] Based on available literature search engine, this case is the fifth reported case worldwide. Most of the patients from published case reports sought consult for chronic cyclic pelvic pain[4,7,9,10], which is different from the patient in this case. This patient reported acute severe abdominal pain that can be attributed to the dextrorotation of the left hemiuteri along with its adhesion to portion of the descending colon and pelvic wall. Adhesions inherent from Mullerian remnants are rarely reported but adhesion arising from adenomyosis result fromof chronic inflammatory process as in the index case. Furthermore, CA 125 may also be elevated in a number of relatively benign gynecologic conditions such as endometriosis and adenomyosis. The mechanism of CA 125 elevation is not fully established yet, the peritoneal irritation or stretch can alter the levels.[11]

Although rare, it is possible to develop adenomyosis in a hypoplastic uterus. At present, the etiology of adenomyosis in itself remains a controversy despite numerous investigations. There has been no established etiopathogenesis of adenomyosis but studies mention several possible postulates: The first theory discusses Cullen's proposal.[4] This is said to be a more established view explaining development of adenomyosis through direct invasion of the endometrial mucosa into the uterine musculature. Invasion is described by pathologists as presence of endometrial glands and stroma in at least one third of the thickness of the uterine wall. In the case of this patient, however, this theory does not seem plausible since it has been confirmed histologically that the patient's hemiuteri did not have a functional endometrium.

The second theory is through metaplasia of stromal cells inside the hypoplastic uterus.[4,7,8,10] This hypothesis was suggested by Enatsu, et al., stating that they found endometrium–like tissues in the myometrium of a patient who did not have a functional endometrium[4]. In a case report by Hoo, et al, the possibility of metaplasia of the stromal cells under the influence of autocrine and paracrine factors mediating genetic, immunologic and endocrine can lead to adenomyosis in situ[7]. Furthermore, Chun et, al. proposed the possibility of spontaneous hyperplasia of ectopic endometrium independent of eutopic endometrium in a patient with normal endometrial cavity. Intraoperative findings and histology report of the index case reinforce adenomyosis arising from the differentiation of stromal cells within the uterine remnants.

The patient and her husband were counselled regarding fertility. Options for having children include adoption and maternal surrogacy[2], however, the latter is still unacceptable in the country. Furthermore, the patient is already 42-years-old and probably had a marginal ovarian reserve. Should she have consulted at an earlier age, her reproductive potential could have been maximized. At present, leaving the ovaries behind enables her to reach menopause naturally.

CONCLUSION

Although rare, development of adenomyosis even in the absence of a functional endometrium is possible. In patients with MRKH syndrome presenting with abdominal pain, thorough evaluation should be done through clinical findings and imaging modalities (ultrasonographic and MRI findings) to guide management. Excision of

mullerian remnants is necessary if becomes pathologic. In addition, women with primary amenorrhea should be carefully assessed to determine the cause. Counselling should always be provided as the condition can be debilitating physically, emotionally and economically. Fertility options such as surrogacy and adoption should be addressed because individuals with MRKH can still have the chance to build her own family. ■

REFERENCES

1. Fontana L. Gentilin B, Fedele L, Gervasini C, MIozz M. Genetics of Mayer-Rokitansky-Kuster-Hauser (MRKH) *Syndrome Clin Genet*. 2017; 91:233-46.

2. ACOG Committee Opinion No. 728: Müllerian Agenesis: Diagnosis, Management, And Treatment. *Obstetrics and Gynecology*. Vol 131. No. 1, January 2018.

3. Abbott JA. Adenomyosis and Abnormal Uterine Bleeding (AUB-A)-Pathogenesis, diagnosis, and management. Best Practice Research. *Clin Obstet Gynaecol*. 2017; 40:68. Epub 2016 Sep 30.

4. Enatsu A, Harada T, Yoshida S, Iwabe T and Terakawa N. Adenomyosis in a patient with the Rokitansky-Kuster-Hauser Syndrome. Fertility and Sterility, vol 73, no 4, pp 862-863, 2000.

5. Lamarca M, Navarro R, Ballesteros M, Aguirre S, Conte M, Duque J. Leiyomyomas in both uterine remnants in a woman with the Mayer- Rokitansky-Kuster-Hauser Syndrome. *Fertility and Sterility.* Vol 91, No.3, March 2009.

6. Amaratunga T. Kirkpatrick I, Yan Y, Karlicki F. Ectopic Pelvic Fibroid in a Woman with Uterine Agenesis and Mayer-Rokitansky-Kuster-Hauser Syndrome. Ultrasound Quarterly. Vol 33. No. 3. September 2017.

7. Hoo PS, Norhaslinda AR, Reza JN. Case Report. Rare Case of Leiomyoma and Adenomyosis in Mayer-Rokitansky-Kuster-Hauser Syndrome. *Case Reports in Obstetrics and Gynecology*. Volume 2016.

8. Chun S, Jeon H, Cho J, Kim M, and Ji I. Endometrial Hyperplasia in Myometrium of Woman with uterine adenomyosis: a case report. *Reproductive Biology and Endocrinology*. Vol. 4, No. 1 pp 56-60. 2012.

9. Meera D, Rani GU, Syamala O. Adenomyosis in a Rudimentary Horn of a Mayer-Rokitansky-Kuster-Hauser Syndrome. 10.505/jp-journals-10032-1055.

10. M.Y. Choi and M. M. Ka. Uterine fibroids and adenomysis in a woman with Rokitansky-Kuster-Hauser syndrome. *Journal of Obstetrics and Gynaecology*, Vol. 22, no. 5, pp. 561-562, 2002.

11. Kil Kicheol, Chung Jae-Eun, Pak Ho Jeong, et.al. Usefulness of CA 125 in the the differential diagnosis of uterine adenomyosis and myoma. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2015 (185)131-135.