Syntax Literate: Jurnal Ilmiah Indonesia p–ISSN: 2541-0849
e-ISSN: 2548-1398
Vol. 7, No. 5, Mei 2022

A CASE REPORT GONADAL HYPOPLASIA CO-EXISTENCE WITH MULLERIAN AGENESIS IN 46,XX FEMALE

Heri Farnas, Dedy Hendry
Faculty of Andalas University /dr. M. Djamil Hospital Padang, Indonesia
Email: farnasheri@gmail.com, dedyhendry1976@gmail.com

Abstract

Introduction: The association or Co-existence of gonadal hypoplasia and Mullerian agenesis is a very rare case. Case Report: We report a 26-year-old phenotypical female presented with primary amenorrhea and underdeveloped secondary sexual characteristics. The hormonal evaluation revealed hypogonadotropic hypogonadism Her karyotype was 46, XX. Diagnostic laparoscopy of the pelvis revealed hypoplasia of the uterine, fallopian tubes, and bilateral ovaries. There were no other morphological malformations. Conclusion: The pathogenesis of the association of Gonadal Hypoplasia Coexistence with Mullerian Agenesis is still mysterious. The treatment is based essentially on hormone substitution therapy and surgical procedure to create neo-vagina for sexual function. The fertility prognosis is unfortunately compromised.

Keywords: gonadal hypoplasia; mullerian agenesis; hypogonadism; primary amenorrhea

Introduction

Gonadal dysgenesis or hypoplasia in females is defined as absent or insufficient development of ovaries. The patient with gonadal dysgenesis presents with primary amenorrhea and lack of development of secondary sexual characteristics due to the inability of ovaries to produce sex steroids. The karyotype in patients with gonadal dysgenesis can be 46XX, 45XO, mosaicism, or deletion of a particular part of X chromosome (Shah et al., 2013), (Jha, Manandhar, & Shrivastava, 2019).

Mullerian agenesis, also referred Mayer-Rokitansky-Küster-Hauser syndrome, or vaginal agenesis. Müllerian agenesis is caused by embryologic underdevelopment of the Mullerian duct, with resultant agenesis or atresia of the vagina, uterus, or both. The female with MRKHS has normal secondary sexual characteristics due to normally functioning ovaries. It is the second most common cause of primary amenorrhea. The co-existence of gonadal dysgenesis and MRKHS, though it has been reported, remains rare (Shah et al., 2013), (Care, 2018).

Gonadal dysgenesis most common Turner syndrome and MRKHS are the 2 most common causes of primary amenorrhea. Although MRKH syndrome and Turner syndrome have the incidence of 1:4500-5000 and 1:2500 in female live births,

respectively. Few cases have been reported so far regarding the co-existence of both syndromes (Care, 2018), (Shahid, 2020).

Though the association between both of them in one patient is considered as coincidental, some hypothesized based on literature studies were described. We report here a case and reviewed all available literature to highlight clinical presentations, karyotype, and gonadal abnormalities in these patients (Shah et al., 2013), (Bousfiha et al., 2010).

Research Methods

Female 26 years old with chief complaint primary amenorrhoea. The patient is unmarried, has a body height of 148cm and a bodyweight of 51kg norm weight body mass index. Vital signs were normal. From the clinical examination, there were underdeveloped secondary sexual signs, pubic hair, axillary hair, and breasts tanner stage 2. Patients did not have facial dysmorphism, webbing of the neck, and skeletal abnormalities. The patient's intelligence is not disturbed where the patient is well educated (complete her bachelor's degree) and currently works as a junior high school teacher. On inspection of the vagina, the introitus was very small, and it was difficult to distinguish it from the urethral opening. The cervix cannot be clearly identified.

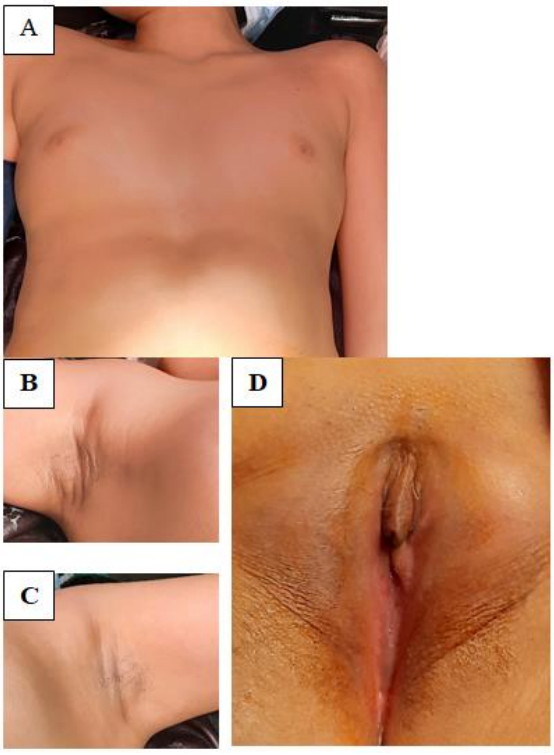

Figure 1
Secondary Sexual Characteristics
(A) Breast, (B) Right axilla, (C) Left axilla,
(D) Pubic Hair and Agenesis Vagina

The complete hematological result did not reveal any abnormalities. Hormonal examinations of female reproductive hormones result in low level FSH, LH, and Estradiol (hypogonadotropic-hypogonadism). Karyotype for chromosome testing shows results of 46XX, which confirmed the patient was female. However, Fluorescence In Situ Hybridization (FISH) analysis was not performed and a partial presence of Y chromosome could not be ruled out.

Table 1
Hormone Profile

Parameter	Result	Reference	Unit
LH ↓	0,16	- Follicular Phase 1st half (D15-D9) : 1,5 – 8,0 2nd half (D8-D2) 2,0 – 8,0 - Ovulation Peak (D0) 9,6-80,0 - Luteal Phase (D+3 – D+15) : 0,2 – 6,5 - Menopause : 8,0 – 33,0	mIU/mL
FSH ↓	0,31	- Follicular Phase: 2,9 – 12 - Follicular Peak : 6,3 – 24,0 - Luteal Phase : 1,5 – 7,0 - Menopause : 17,0 – 95,0	mIU/mL
Estradiol ↓	<9,00	- Follicular : 18-147 - Pre-ovulatory : 93 – 575 - Luteal : 43 – 214 Menopause : <58	pg/mL

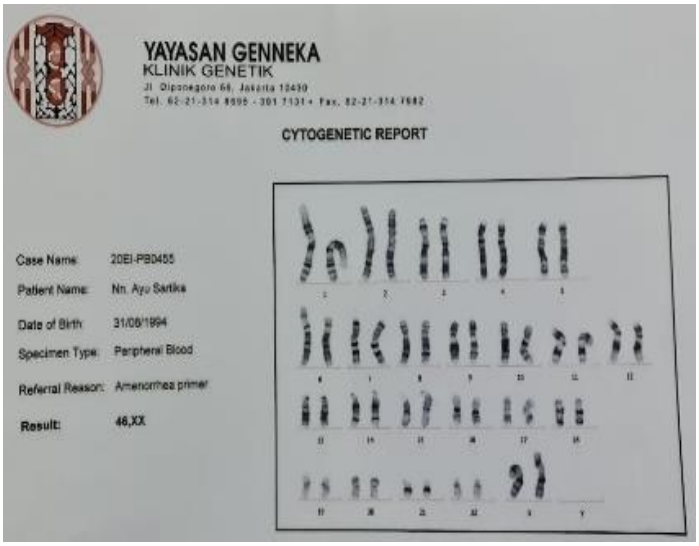

Figure 2
Karyotyping Examination

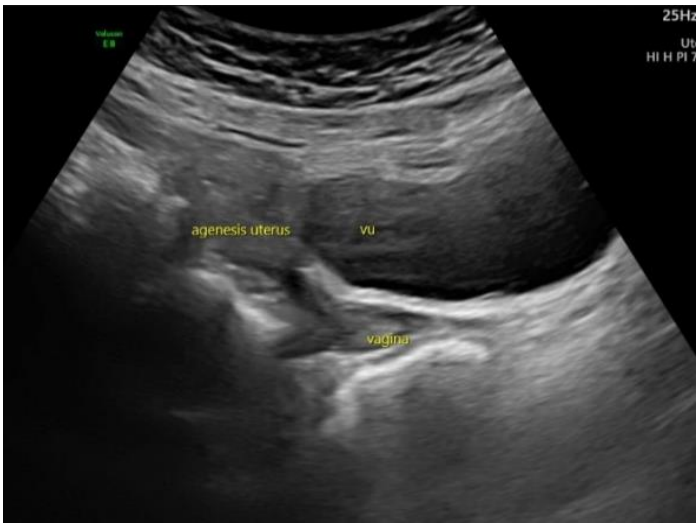

Figure 3
Abdominal Ultrasound Can Not Identify
Uterine And Both Ovaries

From transabdominal ultrasound, both ovaries and uterus are challenging to identify. Furthermore, the patient undergoes diagnostic laparoscopy to provide direct visualization into the internal genital organs. From the diagnostic laparoscopy was seen that the uterus was undeveloped, and both ovaries were hypoplasia.

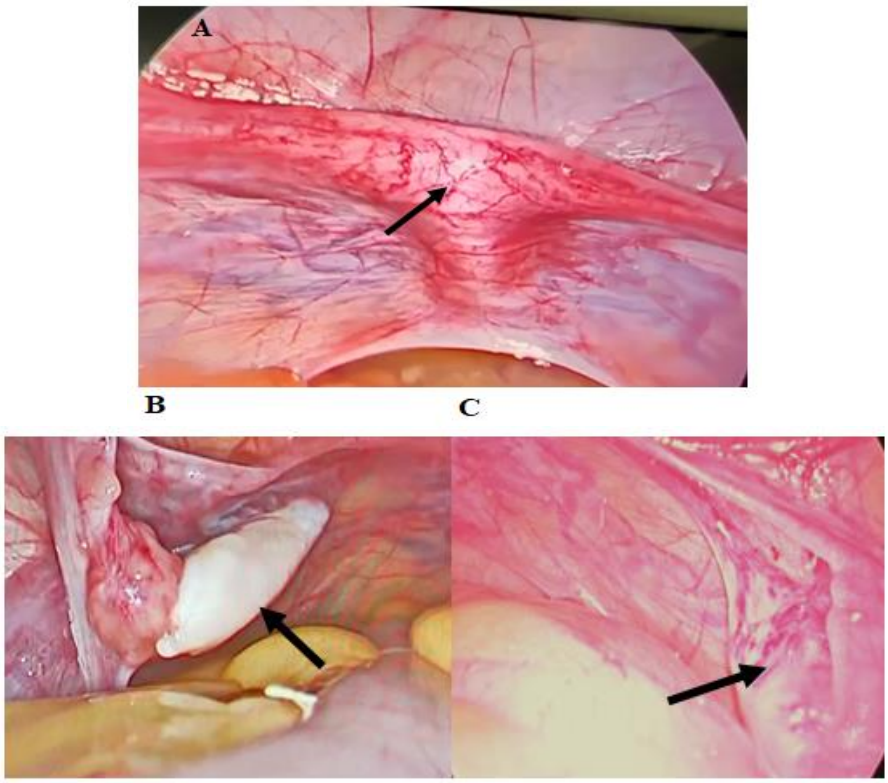

Figure 4
Diagnostic Laparoscopy
(A) Uterine hypoplasia (black arrow)
(B) Left ovary hypoplasia and (C) Right ovary

Results and Discussion

The ovaries embryologically come from 3 sources: the mesodermal epithelium (lining the posterior or abdominal wall), the underlying mesenchyme (embryonic connective tissue) primordial germ cells. The epithelium and mesenchyme proliferate to produce genital ridges (gonads). Primordial germ cells migrate along the dorsal mesentery from the hindgut to the genital ridge and enter the underlying mesenchyme. If primordial germ cells do not form or migrate to the gonadal area, the ovary will not develop (Bousfiha et al., 2010).

MRKHS is characterized by agenesis of Mullerian duct structures, vaginal atresia, an imperfect or absent uterus with normal ovaries and fallopian tubes in normal women of genetic features (46XX). The prevalence has been reported to be 1 in 4,500-5,000 female births (Meena, Daga, & Dixit, 2016). The etiology of MRKHS is not known with certainty but it is believed that embryological development is impaired during the 6 or 7 weeks of pregnancy (Kebaili et al., 2013), (Fontana, Gentilin, Fedele, Gervasini, & Miozzo, 2017) Mutations of the genes coding for antimullerian hormone receptors and a lack of estrogen receptors during embryonic development have been hypothesized to cause MRKHS in which there is a developmental disorder of the Mullerian duct system that will interfere with the development of the uterus, cervix and 2/3 of the vagina (Pizzo et al., 2013).

In this case, the patient had two anomalies, gonadal hypoplasia and accompanied by Mullerian agenesis. The karyotype results obtained 46XX. Gonadal hypoplasia is a primary ovarian defect causing premature ovarian failure in normal 46XX women due to failure of gonadal function to develop or resistance to gonadotropin stimulation. Most of the patients only realized this condition after entering adolescence or young adulthood, with late puberty resulting in primary amenorrhoea Although the underlying etiology of ovarian dysgenesis remains unknown, several genes have been implicated, including homozygous inactivation mutations or compound heterozygotes of the Follicle-Stimulating Hormone Receptor gene (FSHR), mutations in the BMP15 gene, and mutations in the NR5A1.8 gene,12 (Ledig, Röpke, Haeusler, Hinney, & Wieacker, 2008).

Ultrasound examination is often the first diagnostic test in evaluating patients with MRKH syndrome and can confirm the presence of ovaries and the absence of a uterus. However, due to technical difficulties, the results can sometimes be inconclusive. MRI or diagnostic laparoscopy can be used to confirm diagnostic. MRI is the choice of imaging modality of for the confirmation of diagnosis and is also valuable for the identification of any associated malformations (Dandan OA, Hassan A, Alsaihati A, Aljawad L, 2019).

The coexistence of MRKHS and gonadal dysgenesis has been reported in the literature but is extremely rare. The exact genetic mechanisms that underline the association of MRKHS with 46XX gonadal dysgenesis are not known because similar congenital malformations forms of gonadal dysgenesis with coexistent Mullerian agenesis. These patients have an absent or hypoplastic uterus and hypoplasia ovaries

with an agenesis vagina. There is no correlation between chromosomes and phenotypical abnormalities. Some parts of the X-chromosome or transcription factor or protein might have a role in regulating the skeletal, genital, urinary, and gonadal development, and deletion or mutation of that regulatory gene or its product may be responsible for the coexistence of gonadal dysgenesis and MRKHS in an individual (Shah et al., 2013), (Kisu et al., 2019), (Gorgojo, Almodóvar, López, & Donnay, 2002).

Endocrine examination shows a decrease in the levels of FSH, LH and estradiol hormones (hypogonadotropic-hypogonadism) in this condition, the abnormalities that occur could be originated from the hypothalamus-pituitary axis, so that further examination of the Brain MRI needs to be considered (Shah et al., 2013), (Hugh S. Taylor, Pal L, 2020).

We could also consider to performed exogenous GnRH for this patient due to endocrine result shows hypogonadotropic hypogonadism and diagnostic laparoscopy shows hypoplasia of the uterine and both ovaries there to stimulate development of this organ, stimulation with the GnRH could be tried. Although the drug also can be used in women with other ovulatory disorders, it is much less often effective, probably because the pituitary has more difficulty interpreting the mixed signals of endogenous and exogenous GnRH stimuli. In women with primary hypogonadotropic hypogonadism, a low dose (2.5 μg/pulse) can induce ovulation effectively (Hugh S. Taylor, Pal L, 2020).

Estrogen replacement therapy is needed to promote her secondary sexual characteristics, especially breast development. Alendronate sodium can prevent further osteoporosis. Both the uterine and ovaries of this patient never exposed to sex hormone, resulting not developing normally. Will there be any improvement in the development of the uterine and both ovaries after being given hormonal therapy, or this condition irreversible? This question still needs further analysis and research (Bousfiha et al., 2010), (Afendi et al., 2017).

Treatments for these patients ought to be multidisciplinary, with collaboration of endocrinologists, gynecologists endocrinology reproductive infertility, gynecology surgery, and psychologists. The diagnosis of MRKHS imposes a psychological burden on patients because of the associated infertility and sexual dysfunction. Psychological counseling and support groups is one of the management for this case (Ledig et al., 2008), (Londra, Chuong, & Kolp, 2015).

Patients with MRKHS and gonadal dysgenesis cannot become pregnant with their own uterus and cannot have a genetically linked child. Adoption may be the only option for these patients to have a nongenetic child, although uterus transplantation is now a possibility for women with absolute uterine factor infertility (Kisu et al., 2019).

The goals of long-term treatments are surgical to create a functional neo-vaginal canal with an adequate diameter and length, appropriate axial direction, and normal secretion to accommodate sexual intercourse. Creating a neovagina must be offered to patients only when they are ready to start sexual activity. Of the two main types of procedures, the first one consists of the creation of a new cavity and can be nonsurgical

or surgical. The second is vaginal replacement with a pre-existing canal lined with a mucous membrane like bowel (Menon et al., 2009).

Conclusion

The co-existence of gonadal hypoplasia and Mullerian agenesis is a very rare case, therefore management is somewhat complicated. The pathogenesis of the association of Gonadal Hypoplasia co-existence with Mullerian Agenesis is still mysterious. We cannot explain the association between gonadal hypoplasia and Mullerian agenesis in this patient. Theoretically, a primitive undifferentiated gonad could secrete antimullerian hormone in the early stages of embryogenesis, showing a subsequent regression, but this hypothesis is difficult to accept with no gonosome Y in the karyotype. The knowledge of the autosomal and gonosome genes involved in the Mullerian ducts and ovarian development will make an explanation of this exceptional association feasible. The target of the treatment is to promote the development of secondary sexual characteristics, to prevent osteoporosis, achieved normal sexual function, and psychological support. The multidisciplinary team approach is the main key to the management of this patient.

BIBLIOGRAPHY

Afendi, Nik Rafiza, Hoo, P. S., Mahamooth, Mas Irfan Jaya, Ismail, Ahmad Amir, Rahim, Rahimah Abdul, Omar, Ahmad Akram, & Ibrahim, Adibah. (2017). *Coexistence of Mayer-Rokitansky-Küster-Hauser syndrome with Turner syndrome: A case report*. Google Scholar

Bousfiha, N., Errarhay, S., Saadi, H., Ouldim, K., Bouchikhi, C., & Banani, A. (2010). Gonadal dysgenesis 46, XX associated with Mayer-Rokitansky-Kuster-Hauser syndrome: one case report. *Obstetrics and Gynecology International*, *2010*. Google Scholar

Care, Committee on Adolescent Health. (2018). ACOG Committee Opinion No. 728: Müllerian agenesis: diagnosis, management, and treatment. *Obstet Gynecol*, *131*(1), e35–e42. Google Scholar

Dandan OA, Hassan A, Alsaihati A, Aljawad L, Almejhim F. A. rare form of Mayer Rokitansky Küster Hauser syndrome. (2019). *Case report and review of literature*. Case Reports in Women's Health. Google Scholar

Fontana, Laura, Gentilin, Barbara, Fedele, Luigi, Gervasini, Cristina, & Miozzo, Monica. (2017). Genetics of Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome. *Clinical Genetics*, *91*(2), 233–246. Google Scholar

Gorgojo, Juan José, Almodóvar, Francisca, López, Elena, & Donnay, Sergio. (2002). Gonadal agenesis 46, XX associated with the atypical form of Rokitansky syndrome. *Fertility and Sterility*, *77*(1), 185–187. Google Scholar

Hugh S. Taylor, Pal L, Seli E. Amenorrhea. Speroff's Clinical Gynecologic Endocrinology And Infertility. (2020). *9 ed. Philadelphia* (pp. 821–918). pp. 821–918. Wolters Kluwer. Google Scholar

Jha, Santosh Kumar, Manandhar, Rosina, & Shrivastava, Veena Rani. (2019). Coexistence of gonadal dysgenesis and Mullerian agenesis in a female with 46, XX karyotype: a case report. *JNMA: Journal of the Nepal Medical Association*, *57*(216), 119. Google Scholar

Kebaili, Sahbi, Chaabane, Kais, Mnif, Mouna Feki, Kamoun, Mahdi, Kacem, Faten Hadj, Guesmi, Nouha, Gassara, Hichem, Dammak, Abdallah, Louati, Doulira, & Amouri, Habib. (2013). Gonadal dysgenesis and the Mayer-Rokitansky-Kuster-Hauser Syndrome in a girl with a 46, XX karyotype: A case report and review of literature. *Indian Journal of Endocrinology and Metabolism*, *17*(3), 505. Google Scholar

Kisu, Iori, Ono, Ayumi, Iijma, Tomoko, Katayama, Motoko, Iura, Ayaka, & Hirao, Nobumaru. (2019). Mayer-Rokitansky-Küster-Hauser syndrome with a uterine cervix and normal vagina associated with gonadal dysgenesis in a 46, XX female. *Journal of Obstetrics and Gynaecology Research*, *45*(7), 1386–1390. Google

Scholar

Ledig, Susanne, Röpke, Albrecht, Haeusler, Gabriele, Hinney, Bernd, & Wieacker, Peter. (2008). BMP15 mutations in XX gonadal dysgenesis and premature ovarian failure. *American Journal of Obstetrics and Gynecology*, *198*(1), 84-e1. Google Scholar

Londra, Laura, Chuong, Farah S., & Kolp, Lisa. (2015). Mayer-Rokitansky-Kuster-Hauser syndrome: a review. *International Journal of Women's Health*, *7*, 865. Google Scholar

Meena, Alpana, Daga, Mradul Kumar, & Dixit, Rashmi. (2016). Unusual association of turner syndrome and Mayer-Rokitansky-Küster-Hauser syndrome. *Case Reports*, *2016*, bcr2015212634. Google Scholar

Menon, A., Biswas, M., Kochar, S. P. S., Bal, H., Abhichandani, R., & Singh, S. (2009). Vaginal Agenesis in Mayer Rokitansky Kuster Hauser Syndrome. *Medical Journal, Armed Forces India*, *65*(3), 287. Google Scholar

Pizzo, Alfonsa, Laganà, Antonio Simone, Sturlese, Emanuele, Retto, Giovanni, Retto, Annalisa, De Dominici, Rosanna, & Puzzolo, Domenico. (2013). Mayer-rokitansky-kuster-hauser syndrome: embryology, genetics and clinical and surgical treatment. *International Scholarly Research Notices*, *2013*. Google Scholar

Shah, Viral N., Ganatra, Parth J., Parikh, Rajni, Kamdar, Panna, Baxi, Seema, & Shah, Nishit. (2013). Coexistence of gonadal dysgenesis and Mayer-Rokitansky-Kuster-Hauser syndrome in 46, XX female: A case report and review of literature. *Indian Journal of Endocrinology and Metabolism*, *17*(Suppl1), S274. Google Scholar

Shahid, Mohammad Moin. (2020). MRKH syndrome and Turner syndrome co-existing iShahid, Mohammad Moin. (2020). MRKH syndrome and Turner syndrome co-existing in a patient with primary amenorrhoea. Sri Lanka J Diabetes Endocrinol Metab, 10(1), 30–33.n a patient with primary amenorrhoea. *Sri Lanka J Diabetes Endocrinol Metab*, *10*(1), 30–33. Google Scholar