Mullerian agenesis or Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is characterized by congenital aplasia of the uterus and the upper part (2/3) of the vagina in a woman with normal development of secondary sexual characteristics and a normal 46,XX karyotype. It affects 1 in 4500 women, and the usual clinical presentation is primary amenorrhea in a young woman with normal external genitalia and functional ovaries. The phenotypic manifestations of MRKH syndrome may sometimes overlap with various other syndromes and require accurate delineation. The coexistence of both these disorders is extremely rare. Here, we report a case of 46,XX gonadal dysgenesis and MRKH syndrome with anatomically dispersed congenital anomalies unique among reported cases.

KEY WORDS: 46,XX gonadal dysgenesis, hypergonadotropic hypogonadism, Mayer-Rokitansky-Kuster-Hauser syndrome, primary amenorrhea

INTRODUCTION

46,XX gonadal dysgenesis is a rare genetically heterogeneous disorder characterized by underdeveloped ovaries with consequent, imuberism, primary amenorrhea, and hypergonadotropic hypogonadism. Mullerian agenesis or Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is characterized by congenital aplasia of the uterus and the upper part (2/3) of the vagina in a woman with normal development of secondary sexual characteristics and a normal 46,XX karyotype. The phenotypic manifestations of MRKH syndrome may sometimes overlap with various other syndromes and require accurate delineation. Even though previously this syndrome was considered as a sporadic anomaly, increasing number of familial cases now support the hypothesis.
of a genetic cause. We report here a rare case of 46,XX gonadal dysgenesis and mullerian agenesis.

CASE REPORT

A 20-year-old female patient presented to our hospital with complaints of primary amenorrhea, short stature, and absence of secondary sexual characters. There was no family history of consanguinity, miscarriages, neonatal deaths, or any other family member with primary amenorrhea. Her birth, perinatal, and neonatal periods were uneventful. She gives history of delayed milestones and stunted growth from the age of 4 years. Her height was 134 cm and weight 28 kg with normal intelligence. Her pulse rate was 86 beats/min and blood pressure was 100/70 mm of mercury. On cardiac auscultation, a systolic murmur was heard in the aortic area. Scoring of pubic, axillary hair growth, and breast development were Tanner's Stage 1 [Figure 1]. External genital examination revealed immature labia majora and minora, clitoris with a blind vaginal pouch. There was no facial dysmorphism, webbing of neck, or wide carrying angle. There was gibbus in the lumbar region with short fourth metatarsal in the left foot. X-ray of the cervical, dorsal, and lumbar spine revealed fusion of L1 and L2 vertebrae and scoliosis of dorsal spine with no abnormalities in cervical spine [Figure 2]. Echocardiography revealed dilated aorta and bicuspid aortic valve with no other cardiac abnormalities, and abdominal ultrasound examination revealed single horseshoe-shaped kidney and absence of uterus and ovaries. The abdominal ultrasound findings were confirmed later by magnetic resonance imaging (MRI) of the abdomen and pelvis [Figure 3]. T2-weighted coronal image of pelvis revealed bladder and rectum without interposition of uterus. Bilateral ovaries are also not seen in the adnexa. T1-axial fluid attenuation inversion recovery image of the brain at the level of pituitary fossa was normal and karyotyping revealed normal 46,XX complement [Figures 4 and 5]. She was mildly anemic with normal differential count. Her renal and liver function tests were also normal. Endocrine evaluation revealed elevated levels of follicle-stimulating hormone (77 IU/L) and luteinizing hormone LH (37 IU/L) with low estradiol (<5 pg/ml) levels. Her blood sugar, thyroid function tests, serum cortisol, and prolactin levels were normal. Hormonal therapy with ethinyl estradiol 10 µg/day was started for the development of secondary sexual characteristics and to prevent osteoporosis.

DISCUSSION

Gonadal dysgenesis with female phenotype is defined as the absence or incomplete development of ovaries. It is the most common cause of primary amenorrhea. The karyotypes, 45,XO, 45,X/46,XX, 45,X/46, X, dic(X), 46,XX, and 46,XY, have been reported in literature. 46,XX gonadal dysgenesis is relatively rare form of gonadal dysgenesis and wide variations are seen in its clinical presentation.[1,3] Both sporadic and familial cases show these clinical variations. MRKH syndrome is the second most common cause of primary amenorrhea and more commonly presents with only mullerian agenesis and rarely with many other congenital anomalies. The association of gonadal dysgenesis and MRKH syndrome is extremely rare. In the present case, both gonadal agenesis and mullerian agenesis existed in the
same patient along with multiple congenital malformations. Overlapping association of short stature, cardiac, renal, and bony anomalies is seen in both gonadal dysgenesis with Turner’s phenotype and Type 2 MRKH syndromes. The exact genetic mechanisms that underlie the association of 46,XX GONADAL dysgenesis with MRKH syndrome is not known as similar congenital malformations were also seen in cases with 45X0 and mosaic forms of gonadal dysgenesis with coexistent mullerian agenesis.[4,5] Embryologically, ovaries develop from three sources: Mesodermal epithelium, underlying mesenchyme, and primordial germ cells. The mullerian ducts appear lateral to gonads and develop into fallopian tubes uterus and upper part of vagina and broad ligaments. Shah et al. proposed three possibilities for the coexistence of 46,XX gonadal dysgenesis and MRKH syndrome: Mutations or deletions in genes commonly involved in the development and migration of germ cells and mullerian ducts, microdeletions or duplications in X chromosomes resulting in abnormal gene transcription factors interrupting the development of both germ cells and mullerian structures, and endocrine disruptors playing a role.

Literature search revealed few such cases with 46,XX gonadal dysgenesis and MRKH syndrome, and the salient clinical features were discussed here for comparison. Levinson et al. described the first case of 46,XX gonadal dysgenesis and MRKH syndrome in a 17-year-old female who presented with short stature, absence of vagina, secondary sexual characters, internal genitalia, and gonads.[6] Bousfiha et al. reported a case of 46,XX gonadal dysgenesis and MRKH syndrome in which prominent features were normal stature, primary amenorrhea, impuberism with ovarian dysgenesis, absent uterus, and fallopian tubes. No facial and skeletal abnormalities were seen in this case.[7] Bhandari and Chaudhary reported a case from Dehradun, and the clinical findings of this case were short stature, impuberism, rudimentary vagina, and absent uterus and ovaries.[8] Kebaili et al. and Shah et al. described similar cases of 46,XX gonadal dysgenesis and mullerian agenesis without any other congenital malformation in women with normal stature.[9,10] Recently, Dutta and Taneja et al. reported a case of a 19-year-old female from New Delhi with short stature, normal secondary sexual characters, webbed neck, fusion of cervical vertebrae, scoliosis, atrial septal defect, right renal agenesis with malrotated left kidney, and mullerian agenesis.[11] Gorgojo et al. reported a case of a 17-year-old female with 46,XX gonadal dysgenesis and MRKH syndrome with torticollis, lumbar scoliosis, prominent nevi on face and trunk, poorly developed secondary sexual characters, ectopic pelvic kidney, and absence of gonads and internal genitalia with a blind vagina.[12] Oyer et al. reported a case of neonate with 46,XX gonadal dysgenesis who presented with diaphragmatic hernia, doomed bicuspud aortic valve, and mullerian derivative defects.[13] Kennerknecht et al. reported a 19-week-old fetus with 46,XX karyotype, normal
female external genitalia, complete gonadal agenesis, large encephalocele, spina bifida, and omphalocele.\textsuperscript{[14]} All the studies mentioned above revealed that 46,XX gonadal dysgenesis with mullerian agenesis commonly presents with normal female phenotype with primary amenorrhea, impuberism, and hypergonadotropic hypogonadism with or without somatic malformations, the latter being extremely rare. The last two case reports suggest that some of the congenital anomalies may not be compatible with normal survival and this might be the reason for the rarity of these cases.

**CONCLUSIONS**

Both 46,XX gonadal dysgenesis and mullerian dysgenesis are heterogeneous disorders with rare coexistence and obscure reason. It is unclear whether the somatic malformations and ovarian failure are caused by ostensibly pleiotropic gene(s) or closely linked genes.\textsuperscript{[1]} In the present case, a clinical diagnosis of Turner’s syndrome was made initially as patient presented with short stature, primary amenorrhea, and endocrine evaluation revealed hypergonadotropic hypogonadism. Pelvic and abdominal ultrasound revealed absence of internal genitalia and ovaries. Later, MRI scan images confirmed mullerian agenesis and other congenital malformations, and karyotyping has shown 46,XX complement. Hence, the final diagnosis or 46,XX gonadal dysgenesis and MRKH syndrome was made.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Simpson J. XX Gonadal Dysgenesis and Premature Ovarian Failure in 46, XX Individuals Glob. libr. Women’s Med 2008; DOI 10.3843/GLOWM.10355.
2. Morcel K, Camborieux L; Programme de Recherches sur les Aplasies Müllériennes, Guerrier D. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. Orphanet J Rare Dis 2007;2:13.
3. Aittomäki K. The genetics of XX gonadal dysgenesis. Am J Hum Genet 1994;54:844-51.
4. Vadddadi S, Murthy RS, Rahul CH, Kumar VL. A rare case of Turner’s syndrome presenting with mullerian agenesis. J Hum Reprod Sci 2013;6:277-9.
5. Dasgupta S, Mukhopadhyay P, Sharma PP, Begum N, Kalra A. Mayer-Rokitansky-Kuster-Hauser type-b anomaly with MURCS association and gonadal dysgenesis. J Obstet Gynaecol India 2012;62 Suppl 1:83-4.
6. Levinson G, Zárate A, Guzmán-Toledano R, Canales ES, Jiménez M. An XX female with sexual infantilism, absent gonads, and lack of Müllerian ducts. J Med Genet 1976;13:68-9.
7. Boushliha N, Errarhay S, Saadi H, Ouldin K, Bouchikhi C, Banani A. Gonadal dysgenesis 46, XX associated with Mayer-Rokitansky-Kuster-Hauser syndrome: One case report. Obstet Gynecol Int 2010;2010:847370.
8. Bhandari B, Chaudhary BK. Gonadal dysgenesis and the Mayer-Rokitansky-Kuster-Hauser syndrome in a girl with a 46, XX karyotype: A case report. Int J Contemp Pediatr 2015;2:246-8.
9. Kebali S, Chaabane K, Mnif MF, Kamoun M, Kacem FH, Guesmi N, et al. 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 J Endocrinol Metab 2013;17:505-8.
10. Shah VN, Ganatra PJ, Parikh R, Kamdar P, Baxi S, Shah N. Coexistence of gonadal dysgenesis and Mayer-Rokitansky-Kuster-Hauser syndrome in 46, XX female: A case report and review of literature. Indian J Endocrinol Metab 2013;17 Suppl 1:S274-7.
11. Dutta D, Taneya A. Turner like dysmorphia as presenting feature of type-II Mayer-Rokitansky-Kuster-Hauser syndrome. Indian J Med Res 2016;143:378-9.
12. Gorgojo JJ, Almodovar F, López E, Donnay S. Gonadal agenesis 46, XX associated with the atypical form of Rokitansky syndrome. Fertil Steril 2002;77:185-7.
13. Oyey CE, Ramos D, Shoji T, Tantravahi U. 46, XX gonadal agenesis in a neonate with multiple congenital anomalies: Case report and review of the literature. Pediatr Pathol 1994;14:967-72.
14. Kennerknecht I, Mattfeldt T, Paulus W, Nitsch C, Negri G, Barbi G, et al. XX-agonadism in a fetus with multiple dysraphic lesions: A new syndrome. Am J Med Genet 1997;70:413-4.