MIXED GONADAL DYSGENESIS: A CASE REPORT

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ABSTRACT

A 16-year-old girl came to the Gynecology Polyclinic at Haji Adam Malik General Hospital, Medan, complaining of primary amenorrhea. The patient never experienced cyclical abdominal pain or enlargement or lump in the abdomen. Breast growth is found to be in Tanner stage III and pubic hair growth is in Tanner stage II. The patient's height is lower compared to women of her age. The patient weighs 43 kg and is 135 cm tall. Laboratory tests revealed increased levels of FSH, LH, and estrogen. Testosterone levels are within the normal range. Transrectal ultrasound examination revealed uterine hypoplasia with anteflexed uterine position measuring 25.8 x 20.1 x 10.9 mm. The thickness of the endometrium and the left and right ovaries is difficult to assess. The patient then underwent a pelvic MRI examination and found a reduction in the uterus with a volume of 3.43 x 5.54 x 1.45 x 0.523 x 16.69 cm. The endometrium appears to have irregular border. The patient is then planned to carry out a karyotyping examination. From the results of the examination, it was found that the karyotype was 45X / 46 XY. This patient was then diagnosed with mixed gonadal dysgenesis (MGD) and managed with combined contraceptive pills for 3 months.

Keyword: *Mixed gonadal dysgenesis, Disorder of Sex Development, amenorrhea*

1. INTRODUCTION

Mixed gonadal dysgenesis (MGD) is a term used to describe individuals with mosaic chromosomes as well as dysgenetic gonads and varying internal and external reproductive anatomy.[1] MGD refers to individuals with differentiated gonads on one side and gonad streak or testis streak on the other. Some authors apply the term to a patient showing testicular differentiation on both sides with a bilateral testis streak or bilateral dysgenetic testis with a 45X/46XY karyotype. This condition involves a heterogeneous group of gonadal abnormalities and phenotypes with a wide clinical spectrum. The phenotype depends on the ratio of testicular tissue that induces virilization.[2]

Mixed gonadal dysgenesis(MGD) occurs as a result of numerical sex chromosome abnormalities that cause abnormal gonadal development. MGD has a wide spectrum of clinical manifestations, but generally appears as ambiguous genitalia. The majority of types are mosaic, and the presence of the 45,X cell line is often associated with a Y chromosome rearrangement.[3]

Sex chromosome mosaicism (45,X/46,XY and variants) occurs with an estimated incidence of 1.5 per 10.000 births and may be due to loss of a Y chromosome due to delayed anaphase or interchromosomal rearrangements. This event is undiagnosed in almost 95% of cases. Ambiguous genitalia in the newborn, mild loss of virilization (e.g. hypospadias) in boys or even typical Turner syndrome in girls can be associated with mosaicism 45,X/46,XY.[4]

2. CASE

A 16-year-old girl came to the Gynecology Polyclinic at Haji Adam Malik General Hospital, Medan, complaining of

primary amenorrhea. The patient never experienced cyclical abdominal pain or enlargement or lump in the abdomen. Breast growth is found to be in Tanner stage III and pubic hair growth is in Tanner stage II. The patient's height is lower compared to women of her age.

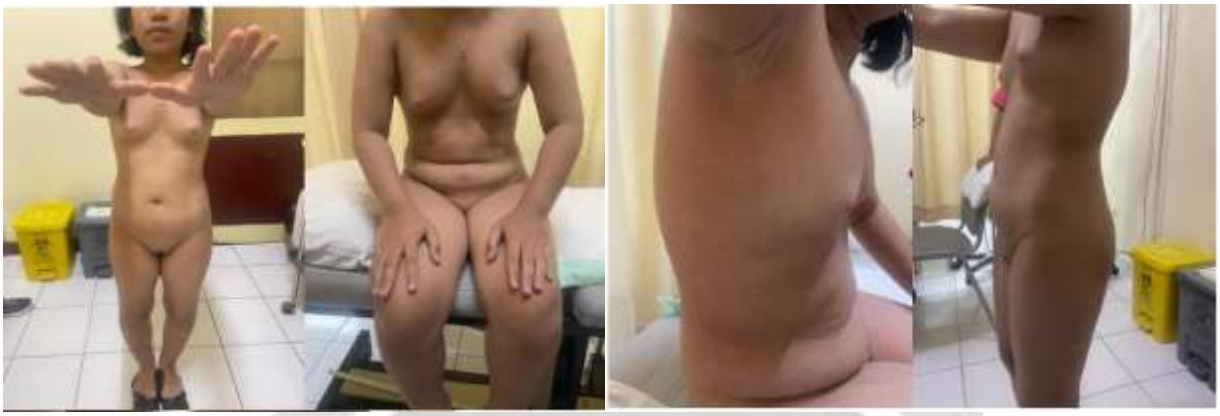

Figure 1. Clinical picture. It appears that the breasts are in Tanner stage III and pubic hair growth is in Tanner stage II.

The patient is the second child of two siblings. He was born full term, was born normally and immediately cried shortly after birth. The patient's birth weight jwas 3500 gr and birth length was 48 cm. She was breastfed until the age of 6 months. The history of menstruation in the patient's mother was at 12 years old. History of growth and development until the age of 5 were according to age.

Examination of vital signs obtained compos mentis consciousness status, blood pressure of 100/60 mmHg, respiratory rate of 20 times/minute, pulse of 90 times/minute, and temperature 36.6°C. The patient weighs 43 kg and is 135 cm tall. Laboratory tests revealed increased levels of FSH, LH, and estrogen. Testosterone levels are within the normal range.

Transrectal ultrasound revealed an uterine hypoplasia with anteflexed uterine position measuring 25.8 x 20.1 x 10.9 mm. The thickness of the endometrium and the left and right ovaries is difficult to assess. The patient then underwent pelvic MRI examination and found a reduction in the uterus size with a volume of 3.43 x 5.54 x 1.45 x 0.523 x 16.69 cm. The endometrium have an irregular margin. The results of the pelvic MRI examination also showed an uterine hypoplasia.

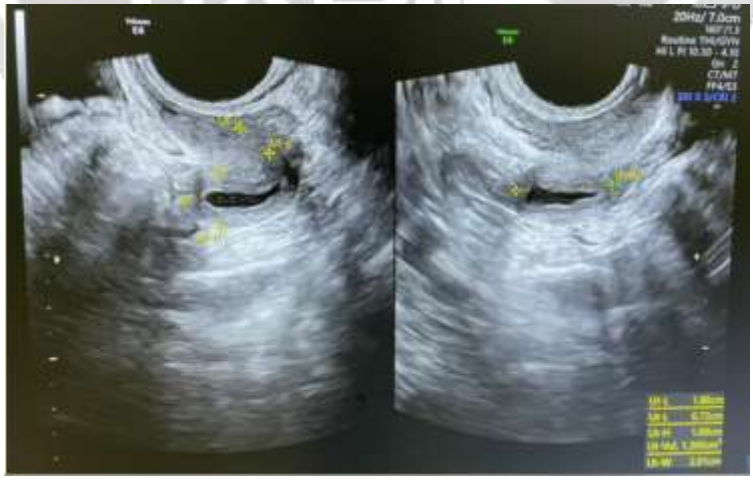

Figure 2. Transrectal ultrasound showed uterine hypoplasia

3. DISCUSSION

Disorders of sexual development (DSD) or sexual development disorders consist of several congenital abnormalities caused by chromosomal, gonadal, and abnormal genital anatomy development. There are several types of DSD based on the etiology. Mixed Gonadal Dysgenesis (MGD) is the second most common cause of DSD causing ambiguous genitalia. Gonadal dysgenesis (ovarian agenesis, gonadal dysplasia) is a clinical syndrome in which secondary sexual characteristics are absent at puberty in women who do not have gonads. Prevalence estimation of gonadal dysgenesis 46,XY is estimated at 1:100,000 births. Phenotype in gonadal dysgenesis 46, XY varies from normal female, ambiguous genitalia to undervirilized male.[5]

Patients with MGD are generally mosaic – the presence of two or more different cell lines in an individual. The classical form of MGD shows 45,X/46,XY mosaicism. The phenotypic manifestations associated with this mosaicism range from infants with ambiguous genitalia to females with the stigmata of Turner syndrome, hypospadias, and gonadal dysgenesis, to a sterile male phenotype. However, this condition cannot be accurately predicted by peripheral blood examination alone, because the mosaic varies in different somatic tissues. The common mechanism for the 45,X/46,XY mosaic variant is loss of a structurally abnormal Y chromosome arising from delayed anaphase during zygotic mitosis. Although Y chromosome abnormalities and interchromosomal rearrangements with abnormal structural Y chromosome loss are occasionally seen, other combinations of currently active chromosome patterns may occur. MGD patients have incompletely developed gonads, which are known as "dysgenetic" or "streak" gonads. Dysgenetic gonads are characterized by varying degrees of maturation or dysfunction, including low sex hormone production.[3]

Normal differentiation of the genitals occurs between 6 – 8 weeks of gestation with the formation of bipotential gonads. This process will continue with differentiation into testicular or ovarian tissue, depending on the ovum cells, which always carry the X chromosome, will be fertilized by sperm with X or Y chromosomes. In order for the activation of this sexual differentiation pathway to occur, several transcription factors that regulate tissue-specific gene expression and signaling molecules must be expressed. Male differentiation was pioneered by SRY (sex-determining region Y) which is encoded on the short arm of the Y chromosome. This gene will produce SRY protein which enables the development of bipotential gonads into testes, among others through the genetic cascade of NR5A1, SOX9, and DAX1 expression. But in the feminization process (XX), there is no SRY gene, thereby activating a cascade of different transcription factors, including WNT4, DAX1, and RSPO1, leading to development of the bipotential gonad into an ovary. Gene expression must be balanced – the genes and their products must be expressed in the right amount, at the right time, and in the right place in the developing embryo. Any mutation or expression imbalance causes DSD.[3]

Individuals with 45,X/46,XY, more specifically patients who have (a specific portion of) the Y chromosome in the karyotype (eventually only at the gonadal level) are at increased risk for development of malignant germ cells, referred to as type II germ cell tumors. This is related to the presence and aberrant expression of testis-specific protein on Y (TSPY), proximal to Yp.[4]

DSD sex chromosomes include conditions 47,XXY (Klinefelter syndrome and its variants), 45,X (Turner syndrome and its variants), 45,X/46,XY (mixed gonadal dysgenesis) and 46,XX/46,XY (chimerism). This condition is often discovered during antenatal care as an incidental finding, with confirmation of the diagnosis after birth. Antenatal diagnosis allows evaluation of other complications frequently associated with the disorder, for example, the cardiac anomaly in Turner syndrome.[6] MGD is generally diagnosed from the neonatal stage through infancy on the basis of abnormal external genitalia, or until puberty on the basis of short stature and primary amenorrhea. MGD is a disease that can be diagnosed based on short stature, abnormal external genitalia, or primary amenorrhea.[7]

The diagnosis is confirmed by cytogenetic analysis of chromosomal status. Karyotype analysis can be performed prenatally after amniocentesis or chorionic villus sampling, postnatally in patients with multiple genitalia, or later in patients with fertility problems. Patients with mixed gonadal dysgenesis 45,X/46,XY (45,X/46,XY MGD) mostly have a 45,X/46,XY karyotype, with the phenotype of the gonads and external genitalia depending on the proportion of monosomic cells. The presence of the 45,X cell line is often associated with rearrangements of the Y chromosome (commonly dicentric and Y-ringed chromosomes), which may also impact phenotype. All cases are sporadic. Several genotype-phenotype correlations have been established: partial expression of the SRY gene (causing partial testicular dysgenesis and resulting in reduced synthesis of testosterone and hence a deficit of androgenization), presence of a gonadoblastoma locus (TSPY1) on the Y chromosome in females (associated with an increased risk of development of neoplasms), and loss of the SHOX gene dose leading to short stature. The formation of the uterus due to lack of production of anti-Müllerian hormone.[8]

Management guidelines divide patients into three groups and treatment strategies namely mild undervirilization in which orchidopexy, biopsy, post-pubertal monitoring and self-examination are carried out every three months;

Ultrasound is done annually; Ambiguous genitalia with a lower threshold for gonadectomy and a female phenotype are recommended for elective gonadectomy. Plans for early gonadectomy, if the gonads cannot be relocated or have already shown signs of malignancy, or delayed gonadectomy depends on hormone secretion, adherence to surveillance and/or patient preference.[1]

In patients with MGD who are raised as girls, bilateral gonadectomy should be performed in childhood or after diagnosis because of the risk of malignancy and suboptimal gonadal function.[9] In addition, external genitalia should be repaired and estrogen therapy should be initiated at normal pubertal age.[10]

4. CONCLUSIONS

Mixed gonadal dysgenesis (MGD) is a disease that can be diagnosed on the basis of short stature, abnormal external genitalia, or primary amenorrhea. This condition is generally diagnosed no later than puberty. Bilateral gonadectomy should be performed in childhood or after diagnosis because of the risk of malignancy.

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