A Mixed Gonadal Dysgenesis in an 19 Year Old Girl with Ambigous Genitalia: A Case Report

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ABSTRACT

A 19-year-old girl was referred with delayed puberty and ambiguous genitalia. She had short stature with high blood pressure and Turner's stigmata with external genitalia Prader Score 4. Ultrasound revealed hypoplastic uterus with no gonad. Follicle stimulating hormone, luteinizing hormone and testosterone level were increased (51.29 mIU/mL, 23.66 mIU/mL and 742 ng/dl). Karyotyping revealed 46 XY with Fluorescence in situ hybridization cytogenetic study based on 300 cells showed mosaic chromosome, monosomy X (17%) and XY (83%). Laparascopic gonadectomy was done and showed that testes were only in the right inguinal canal. Then patient had external genitalia reconstruction and received estrogen replacement therapy.

Keywords*: mixed gonadal dysgenesis, ambiguous genitalia*

INTRODUCTION

Disorders of sexual development (DSD) are a congenital condition in which the development of the chromosomal, gonadal, or anatomic sex is atypical.[1] These are divided into 46 XX DSD, 46 XY DSD, and sex chromosome DSD.[2] Gonadal dysgenesis is part of DSD and characterized by incomplete or defective gonadal development as a result of either structural or numerical anomalies in the sex chromosomes or mutation in the genes involved.[3] Mixed gonadal dysgenesis (MGD) belongs to sex chromosome DSD, which has a prototypical karyotype of 45,X/46,XY, and many variations in clinical manifestation. We

herein report 19 years old female with MGD presenting with ambiguous genitalia and delayed puberty.

CASE ILLUSTRATION

A 19-year-old "girl", was referred to our hospital by Abdoel Moelek Hospital in Lampung Province, with a suspect of Turner Syndrome. The chief complaint of the patient were delayed menstruation and breast development. Her medical history revealed 38 weeks' gestation with a weight of 2700 gr and length of 48 cm. At birth, atypical "clitoris" as female externa genitalia was found. She was raised as female and had short stature with normal motoric development. The girl had not pubarche and thelarche but had virilization sign as voice deepening at puberty and clitoris become bigger (clitoromegaly). She was also a quite type of person. At presentation aged 19 years, physical examination revealed a height of 135 cm, a weight of 38 kg, body mass index was normal (20.9 kg/m2) and with a potential genetic height of 136.5-156.5 cm. Blood pressure was 145/98 mmHg. She had low hairline, strabismus, hirsutism and wide neck. She showed a normal cardiopulmonary and abdominal examination; no intra-abdominal or inguinal masses were palpable. External genitalia inspection revealed a marked clitoromegaly, labia enlargement resemble scrotum with no testes and introitus vaginal. The Tanner stage was pubic hair II, breast I, axillary hair I. The Prader Stage was 4. The karyotyping examined based on 20 cells showed 46 XY. Testosterone level was 742 ng/dl (8.4-48.1 ng/dl) and DHEA level was 95.3 ug/dl (61.2-493.6). Luteinizing Hormone (LH) was 23.66 mIU/mL (2.4-12.6), Follicle Stimulating Hormone (FSH) was 51.29 mIU/mL (3.5-12.5) with normally 17 OH progesterone and cortisol (2.68 ng/ml and 15.6 ug/dl) and decrease of Anti Mullerian Hormone (AMH) (1.64 ng/ml). Renal function (eGFR) was decreased (33.6 mL/min/1.73 ml). Bone age revealed average 18 years old girl. Abdominal CT revealed undescended testes only in right inguinal canal and hypoplasia uterus. There was no left testes and ovarium founded. Abdominal doppler vascular ultrasound revealed suspicious of proximal renalis artery stenosis. Then patient was referred for Fluorescence in situ hybridization (FISH) test and showed mosaic chromosome, monosomy X (17%), and XY (83%) from 300 cells. Rekaryotyping after FISH examination revealed mos 45,X[2]/46,XY[38]. We make the diagnosis of this patient became mixed gonadal dysgenesis (MGD). The parents were informed about this disorder then referred to a psychiatrist. Gender identity revealed that the patient was adopted as female because she has raised as a girl and has been comfortable with it. She also had moderate mental retardation that made the decision depend on her mother. The patient then undergone the right gonadectomy and external genitalia reconstruction. The biopsy result was atrophic testicular cell without spermatogenesis. Now she receives the estrogen replacement therapy. Psychosocial support was started as soon as the diagnosis was established.

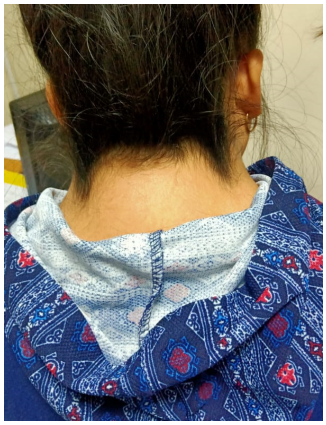

Figure 1. Low Hairline and Web.

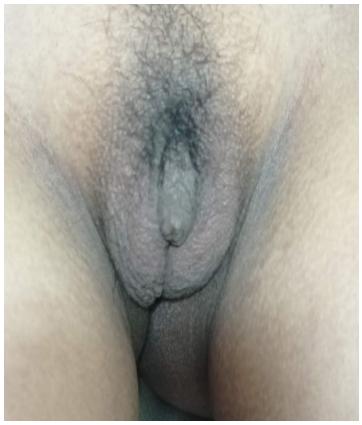

Figure 2. Ambiguous Genitalia.

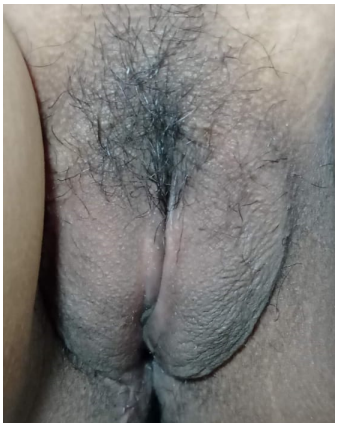

Figure 3. Post Genitalia Reconstruction.

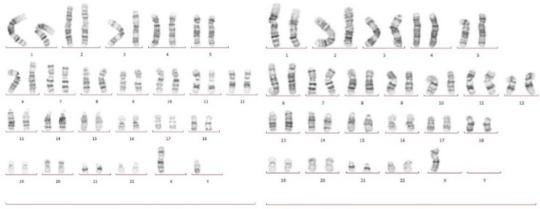

Figure 4. Second Karyotype.

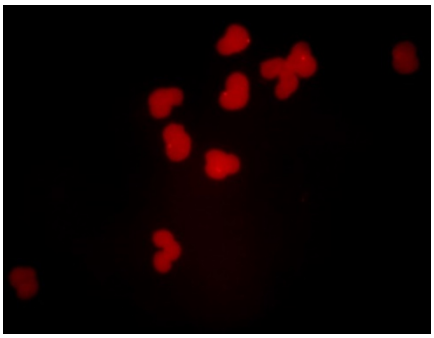

Figure 5. FISH.

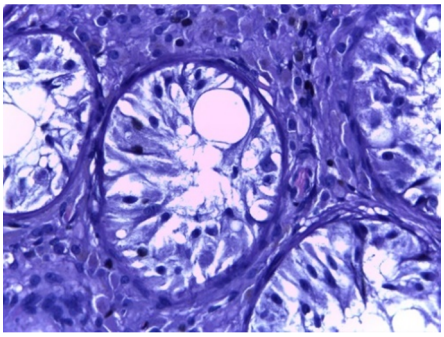

Figure 6. Abundant Leydig Cell Without Spermatogenesis.

DISCUSSION

Ambiguous genitalia is a common term that is used to describe atypical internal or external genitalia. This condition is one of clinical manifestation of DSD. DSD can be defined where the genital is disconcordant with chromosomes or gonads. DSD have 3 categories, 46 XX DSD, 46 XY DSD, sex chromosome DSD.[2]

Our patient had turner's syndrome phenotype with ambiguous genital. Classical Turner's Syndrome never present with ambiguous genital so Congenital Adrenal Hyperplasia (CAH) was first our consideration. The first step that we did was to look genotype of the patient by chromosomal analysis. Standard chromosomal analysis from 20 cells examined revealed 46 XY. The 17 OH Progesterone and cortisol level showed in the normal limit, made CAH could be excluded. Because of a discrepancy between phenotype, biochemical results and imaging, we decided to do second karyotyping with more number of cell and FISH (fluorescence in situ hybridization) to look particular DNA sequence. FISH cytogenetics revealed the presence of XY chromosome in 83% cell and one X chromosome in 17% of cells studied (300 cells). The rekaryotyping was 45,X[2]/46,XY[38], suggestive mixed gonadal dysgenesis (MGD). In this case, the level of mosaicism 45,X/46,XY was low, that could not be detected by standard karyotyping procedure. Analysis of FISH on large numbers of cells helped us to confirm the diagnosis by looking the particular of DNA sequence.[4]

MGD is a rare disorder of sexual differentiation which occurs due to asymmetrical gonadal development and belongs to sex chromosome DSD.[5] MGD commonly has a combination between XO and XY genotype in a cell which showed by karyotype of 45,X/46,XY. The 45,X/46, XY mosaicism is estimated detection rate of 1.7 per 10.000 newborns.[6] It usually happens because of non-disjunction in mitotic phase post zygotic. 45 X appears because of chromosome Y rearrangements (commonly dicentric and ring Y chromosome). Partial testicular dysgenesis on 45,X/46,XY can be happened because of partial expression of the SRY gene made a disturbance of testosterone synthesis with undervirilization. SRY gene provides instruction for making sex determining region Y protein. The presence of Y chromosome in dysgenetic gonad renders the child at high risk to gonadal malignancy (gonadoblastoma) and dosage loss of the SHOX (Short Stature Homeobox) gene that made short stature phenotype. The other features in our patient was uterus existence, which is determined by lack of AMH level which was responsible with the regression of the mullerian ducts, fallopian tubes and uterus.[7]

The clinical symptoms of MGD are combination between XO gonadal dysgenesis and the normal XY male.[5] It varies depends on ratio of 45, X/46, XY fragment among the tissues, with those having a higher ratio being more likely to exhibit the turner syndrome phenotype. We could find a wide spectrum of phenotypes, from turner syndrome to phenotypically normal males. In our patient, 45 X cell (monosomy X) made the presence of the somatic stigmata of turner syndrome's such as short stature, low hairline, strabismus, wide neck, anomaly of renal until mental retardation. MGD patients sometimes have overlapping features of classical Turner syndrome.[8] There were 10-12% cases of Turner Syndrome has 45,X/46,XY mosaicism.[9] Furthermore, high level of testosterone in our patient represent the function of XY cell. The mosaicism ratio in gonadal tissue and blood may explain the variability in the phenotypes.[8] Turner syndrome phenotype in this patient may occur because of the higher ratio of 45,X/46,XY fragment and consequent lack of Y chromosome in her gonadal tissue. Unfortunately, we just measure the ratio only in peripheral lymphocyte. Wu Q et al reported 16 Chinese patients with 45,X/46,XY mosaicism demonstrated that most patients had persistent Mullerian structures with a streak or unidentified gonads which present as an infantile or rudimentary uterus with 2 patients having a normal sized uterus. These findings are consistent with our patient. [10] Anomaly renal also happened in our patient. She has secondary hypertension with chronic kidney failure stage IIIa with suspection of renalis artery stenosis based on doppler vascular abdominal ultrasound. The last, the Turner's mosaicism also explained the hypergonadotropic in this patient.[9]

The average age of onset of puberty in MGD, was from 11 to 13 years, which is within the normal range. It consistently appears with our patient.[7] The genital appearance of MGD is characterized by the asymmetrical testis with unilateral testis dysgenesis, a streak gonad on contralateral side and persistent Mullerian structures.[11] First time, we found clitoromegaly resemble phallic enlargement without visualization of testes by physical examination and ultrasound. So, we conducted abdominal CT and found single testis in dextra canalis inguinalis, uterus hypoplasia and no ovarium. The biopsy showed that there were much leydig cell, but without spermatogenesis process. This explained why our patient had high level testosterone and male sex secondary sign likes deepening voice. Imaging is generally used to evaluate presence localized gonads and detect any malignanty features. However, small tumours or dysgenetic gonads may be missed due to the heterogenecity of their size and appearance.

The multidisciplinary approach, involving endocrinologist, psychiatrist, gynecologist, urologist and biological scientist, is the corner stone for DSD. We conducted a careful review of physical and psychologic features, hormonal evaluation, karyotyping, and imaging. The psychological evaluation revealed female gender identity. We found little difficulties in this process, because this patient had moderate mental retardation. So the decision depends on her mother. This explained why she was so quite when we did some questions.

In the early process, we much considered the balance of risk and benefit of surgery. Our patient was phenotypically dominance of female and has been raised as a female for her whole life. In case of the decision to convert to female gender, testis structures should be removed. So we decided to do laparoscopy gonadectomy and external genitalia reconstruction. The surgical approach also considered about future surveillance and risk of malignancy because dysgenetic gonad. The risk of malignancy particularly gonadoblastoma which caused by the presence of Y chromosome is 7-10% in one study. [9] The risk of developing a malignancy was noted to be highest in individuals with ambiguous phenotype, 52% compared to 2.2% in females without signs of virilization.[12] The histopathological examination revealed the testis contained abundant mature leydig cells and tubules with only sertoli cells but without spermatogenesis process, i.e. the picture of germinal cell aplasia. Post operative, the level of testosterone becomes normal and estrogen replacement therapy was started to stimulate secondary sexual development and uterine growth and prevent bone loss. Follow-up for

the patient should also encompass monitoring of health performance and hormonal replacement. Full of informed consent should be given in family because it can address some stigma in the future.

CONCLUSION

We present a rare disorder of mixed gonadal dysgenesis(45,X/46 XY) with turner's phenotype, ambiguous genital with gender identity of female. This case needs comprehensive management of the rare endocrine condition.

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