ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

REVIEW ARTICLE

46, XX Infertile Male: A Case Report and Review in Infertility

Gito Restiansyah Wasian[1]*, Tjahjo Djojo Tanojo[1], Rina Yudiwati[2], Petrus Supardi[1], Silvia W Lestari[1,3]

1. *Andrology Specialist Program, Medical Faculty of Universitas Airlangga/Dr. Soetomo Hospital Surabaya, Indonesia.*
2. *Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
3. *Department of Medical Biology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.*

***Corresponding Author: Gito Restiansyah Wasian**

Abstract

Introduction: 46, XX Testicular Disorder of Sex Development (46, XX Testicular DSD) is a genetic disorder that can cause male infertility. The clinical feature of this disorder varies, ranging from ambiguous genitalia to normal male genitalia characteristics. This disorder is rarely diagnosed early and is often only found during fertility tests. The objective of this work was to determine the characteristics and managements of patient with 46, XX testicular DSD. Methods: Case report and literature review. Results: A 30-year-old came with complaints of wanting to have children after a 7-year marriage. From physical examination, it was shown normal male external genitalia with small testicular volume. Sperm analysis showed azoospermia. From hormonal examination, hypogonadotropin hypogonadism is obtained. Cytogenetics gives an overview of 46, XX male with positive SRY gene. Conclusion: Patient characteristics vary depending on the mutation that occurs. Furthermore, 46, XX testicular DSD with can be found during holistic infertility examination, such as semen and hormonal analysis and karyotyping and SRY gene detection. A multidisciplinary approach should be performed too in the management, particularly for assisted reproductive technology with sperm donor or adoption.

Keywords: *46, XX male, Testicular DSD, Male infertility, SRY gene.*

Introduction

Infertility is a condition in which a partner fails to conceive after 12 months of regular sexual intercourse, without any contraception [1]. This condition affects at least 15% of couples, and nearly half is related to male factor infertility [2, 3]. Approximately 3-6% of male infertility is caused by genetic factors; including chromosomal abnormalities [3, 4].One of the chromosomal abnormalities is 46, XX male syndrome. 46,XX male syndrome or now known as 46,XX Testicular Disorder of Sex Development, was first reported by De la Chapelle in 1964 [5].

It is found in one of the 20.000- 30.000 men worldwide [6, 11]. Some men with 46, XX have normal male external and internal genitalia, but about 10% are found with hypospadias, and 10-20% with ambiguous genitalia [6, 7]. This disorder are rarely diagnosed early and is oftenly discovered during an infertility examination [8, 10].Various clinical features of this condition are a challenge for the andrologist to be able to establish the diagnosis when examining infertility. In this case report, we will report a male infertility case with 46, XX testicular DSD. This case is the first case at the Andrology unit of Dr. Soetomo Hospital, Surabaya. The aim of this case report is to determine the characteristics and managements of patients with 46, XX testicular DSD.

Case Report

A 30-year-old man came to andrology unit of Dr. Soetomo Hospital, Surabaya in March 2018 with infertility problem. Patient was routinely screened for infertility, including history taking and physical examination. The patient has been married for 7 years. This is his first marriage and has not had children

before. Patient claims to have intercourse 2-3 times every week, and has no problem in sexual activities, such as erectile function and ejaculation. The patient is the first child of 2 siblings which has no family history with similar complaint. There were no routine medications taken and history of diseases that can interfere with gonadal function. From physical examination (Figure 1), the obtained data showed obese body posture, with 2nd degree of gynecomastia.

The upper and lower body part ratio is normal. The spread of pubic hair is in accordance with the tanner V. The penis is normal, with a length of 10 cm and a circumference of 9 cm. The right testis is palpated in the scrotum with a volume of about 2 ml, while the left testis is almost not palpable. Sperm analysis showed the result of azoospermia (post *centrifugation)* with a fructose value of 14.0 (Normal value :> 50) µmol/ejaculate. Furthermore, the hormonal analysis showed an increase in the gonadotropin hormone, namely *luteinizing hormone* (LH) 10.61 (Normal value: 1.5 - 9.3) mIU/ml and *follicle stimulating hormone* (FSH) 28.38 (Normal value: 1.4 - 18.1) mIU/ml, while testosterone levels are low, 113.16 (Normal value: 241-827) ng/dl.

In order to clarify the un-palpabletestis, the ultrasound examination was performed and resulted that the testes were in the right and left scrotal regions, with the right testicular volume of 1.62 ml and left of 1.22 ml. In addition, cytogenetic examination of peripheral blood was demonstrated 46, XX with a positive SRY gene result (Figure 2).

Figure 1: Phenotype of a male patient with 46, XX testicular DSD

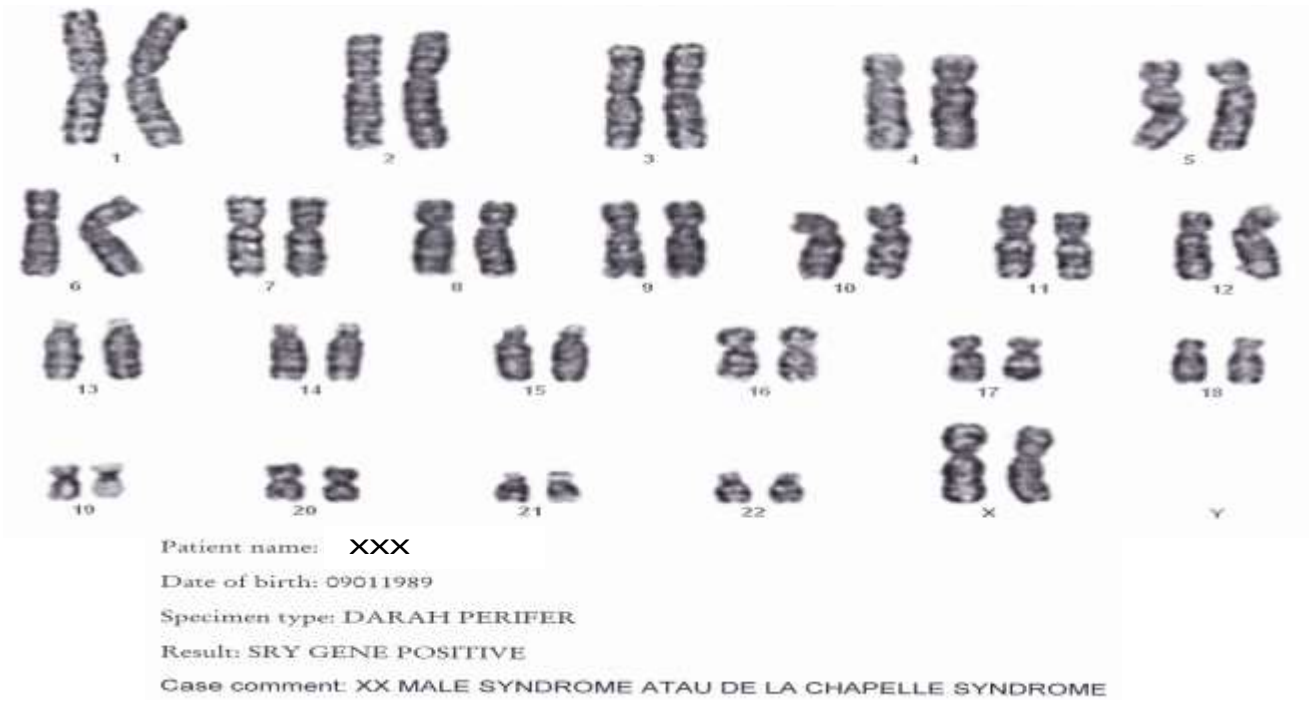

Figure 2: Result of cytogenetic examination of male patient with 46, XX testicular DSD

Discussion

Characteristics of Patients with 46, XX Testicular DSD

In patients with 46, XX testicular DSD, there is a mismatch between genotype (female) and phenotype (male). Most patients have normal external and internal male genitalia, but about 10-20% experience hypospadias to ambiguous genitalia, due to decrease of fetal testosterone production [6, 7]. Testicular histology looks normal in the first year of life, but spermatogonia was not found after the age of one year [6]. In some cases, ovarian tissue can also be found in the testes [9].

These forms of DSD abnormalities can be grouped into SRY-positive and SRY-negative [12, 13]. In approximately 90% of patients can be found SRY gene on the X chromosome paternal [7]. This condition is caused by XY paternal interchange that occurs during paternal meiosis [10, 11]. One-third of all recombinations occur at the PRKX locus at Xp22.3 and the homologue PRKY-Y. (Figure 3) [8, 9, 12].In addition to the translocation of genetic material from the Y chromosome (including the Trans SRY gene), several other mechanisms are thought to cause this condition, namely mutations in the autosomal or X chromosome gene, and Y mosaic line carrier cells [7].

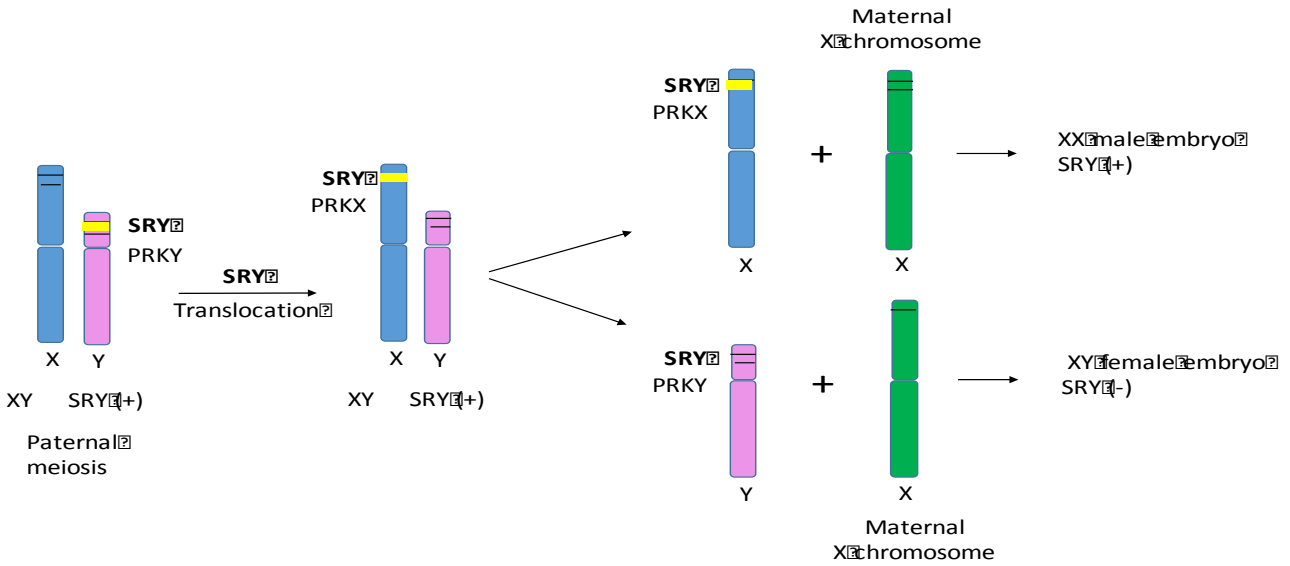

Figure 3: Schematic of pathogenesis of male 46, XX with SRY-positive [9]

Patients with SRY-positive generally have normal male external genitalia, gynecomastia, small testicular azoospermia, hypergonadotropin hypogonadism, and often present with infertility [8, 14, 15].Some lose more sequence of the X chromosome causing short posture or mental retardation; while some with a slight deviation of Y experiencing hypospadias or other abnormalities in the development of other male genitalia [6, 7, 10]. There is no sexual dysfunction in men with 46, XX, with a small to normal phallus size [12].

The molecular etiology of men 46, XX with SRY-negative is more diverse, including overexpression of the SOX10 gene on 22q13, duplication or up regulation of Sox9, over expression of genes *SOX3*, mutations in the loss of RSPO1 gene function, and interference *WNT4* that cause SERKAL syndrome [13, 16, 20].

Diagnosis 46, XX Testicular DSD

In men without ambiguous genitalia, the diagnosis is often made on late puberty examination or infertility. In 46 patients, XX testicular DSD, germ cells did not undergo meiosis, so the examination obtained a small testicular size and azoospermia [9].

Patients with 46, XX testicular DSD will show an increase in FSH and LH level, a decrease in T and DHT level, and less than 2 times the increase in response to the hCG stimulation test. Whereas in patients with ovotesticular DSD, gonads can still function so that the levels of the hormones FSH, LH, estradiol, T, and DHT remain normal [8, 12, 21].Serum AMH level (> 75 pmol / L) is a good biochemical indicators for assessing testicular tissue function [9, 12].

Pelvic ultrasound examinations showed no uterus, and semen analysis showed normal semen volume with azoospermia [8, 12].Cytogenetic examination must be carried out in cases of severe azoospermia or oligospermia, including karyotype and PCR or FISH for detection of *SRY* genes [13, 14, 22].

In patients 46, XX with SRY-negative and ambiguous genitalia, gonadal biopsy is needed to check whether ovarian tissue is found, and to assess the risk of gonadoblastoma [8, 23]. Biopsy results generally found Leydig cell hyperplasia and spermatic failure [24]. In the case of translocation, SRY is needed to evaluate mutations (translocated to the X chromosome or autosomal), because the pattern of heredity and genetic counseling will be different [12].

Management 46, XX testicular DSD

Immediately after establishing the diagnosis, a multidisciplinary approach that focuses on current and long-term issues needs to be performed. General practitioners play a role in assisting patients and providing appropriate referrals to andrologists, endocrinologists, radiologists, and psychiatrists according to patient needs [14, 22, 24, 26].In some patients, androgen replacement therapy is useful for correcting hypogonadism [12].Low dose testosterone replacement therapy can be started immediately in patients over the age of 14 years without contraindications to testosterone therapy. Hematocrit examination needs to be done in the 3rd, 6th, 12th month. Examination of liver function and fat profile is also recommended to be examined before starting therapy, at the 6th month, and annually [22].Surgery can be done to improve ambiguous genitalia and in patients with hypospadias or cryptorchidism [24].Patient with gynecomastia, can experience a reduction in mammoplasty, which is useful for reducing the risk of breast cancer [22].

In patients with 46, XX testicular DSD, no germ cells were found, therefore testicular biopsy for *intracytoplasmic sperm injection* (ICSI) did not provide benefits [8, 12]. Fertility options in patients with 46, XX testicular DSD are very limited. In some countries, reproductive technology can be assisted with sperm donor or adoption can be considered too [22].

Conclusion

In conclusion, patient characteristics vary depending on the mutation that occurs. Furthermore, as a rare cause of infertility, 46, XX testicular DSD with complete masculinization can be found during holistic infertility examination, such as semen and hormonal analysis and karyotyping and SRY gene detection. A multidisciplinary approach should be performed too in the management, particularly for assisted reproductive technology with sperm donor or adoption.

References

1. World Health Organization (2000) WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple. Cambridge: Cambridge University Press.
2. Greenhall E, Vessey M (1990) The prevalence of subfertility: a review of the current confusion and a report of two new studies. Fertil. Steril., 54(6):978-83.
3. Nieschlag E, Behre HM, Nieschlag S (2010) Male reproductive health and dysfunction. In Nieschlag E, Behre HM and Nieschlag S (3rd edition) Andrology. Berlin: Springer Verlag.
4. Seno DH, Birowo P, Rasyid N, Taher A (2011) Etiologies of Male Infertility in Dr. Cipto Mangunkusumo. Indones. J. Obstet. Gynecol., 35(3):130-4
5. De la Chapelle A, Hortling H, Niemi M, Wennstroem J (1964) XX sex chromosomes in a human male. First case. Acta Med. Scand, 175: 25.
6. Remeithi SA, Wherrett DK (2015) Disorders of Sex Development. Fanaroff and Martin's Neonatal-Perinatal Medicine 10th Ed, 98: 1516-1552. Saunders.
7. Diamond DA, Yu RN (2016) Disorders of Sexual Development: Etiology, Evaluation, and Medical Management. Campbell-Walsh Urology 11th Ed, 150: 3469-3497.e6. Elsevier.
8. Witchel SF, Topaloglu AK (2019) Puberty: Gonadarche and Adrenarche . Yen & Jaffe's Reproductive Endocrinology, Chapter 17: 394-446.e16.

9. Rey RA, Josso N (2016) Diagnosis and Treatment of Disorders of Sexual Development. Endocrinology: Adult and Pediatric 7th ed, Chapter 119: 2086-2118.e5. Saunders.
10. Ali O, Donohue PA (2020) Hypofunction of the Testes. In Nelson Textbook of Pediatrics. Chapter 601: 2993-3000.e1. Elsevier
11. Kolon TF (2014) Disorders of Sexual Development. In Penn Clinical Manual of Urology 2nd ed. Chapter 27: 775-775. Saunders.
12. Délot EC, Villain E (2019) Disorders of Sex. Yen & Jaffe's Reproductive Endocrinology 8th ed, Chapter 16: 365-393.e5. Elsevier.
13. Achermann JC, Hughes IA (2016) Pediatric Disorders of Sex Development. Williams Textbook of Endocrinology 13th Ed, Chapter 23: 893-963. Elsevier.
14. Chakraborty PP, Bhattacharjee R, Roy A, Mukhopadhyay S, Chowdhury S (2016) Male Factor Infertility: Clues to Diagnose 46, XX Male. The Journal of Obstetrics and Gynecology of India, 66(S2):S662-S665.
15. Kim MS, Hwang PH, Lee DY (2015) A 46, XX Male Adolescent Presenting with a Chief Complaint of Gynecomastia. Pediatrics and Neonatology, 56: 357-359.
16. Xiao B, Ji X, Xing Y, Chen Y, Tao J (2013) A rare case of 46, XX SRY-negative male with a w74-kb duplication in a region upstream of SOX9. European Journal of Medical Genetics, 56: 695-698.
17. Kim JW, Bak CW, Chin MU, Cha DH, Yoon TK, Shim SH (2010) SRY-negative 46,XX infertile male with Leydig cell hyperplasia: clinical, cytogenetic, and molecular analysis and review of the literature. Fertility and Sterility, 94: 2.
18. Alves C, Braid Z, Coeli FB, de Mello MP (2010) 46, XX Male-Testicular Disorder of Sexual Differentiation (DSD): hormonal, molecular and cytogenetic studies. Arq Bras Endocrinol Metab., 2010: 54-8.
19. Dorsey FY, Hsieh MH, Roth DR (2009) 46, XX SRY-Negative True Hermaphrodite Siblings. Urology, 73: 3.
20. Alchamat GA, Alhlabi M, Issa M (2010) A case report of an XX male with complete masculinization but absence of the SRY gene. Middle East Fertility Society Journal, 15: 51-53.
21. Chiang HS, Wu YN, Wu CC, Hwang JL (2013) Cytogenic and molecular analyses of 46,XX male syndrome with clinical comparison to other groups with testicular azoospermia of genetic origin. Journal of the Formosan Medical Association, 112: 72-78.
22. Ryan NAJ, Akbar S (2013) A case report of an incidental finding of a 46,XX, SRY-negative male with masculine phenotype during standard fertility workup with review of the literature and proposed immediate and long-term management guidance. Fertility and Sterility, 99: 5.
23. Minor A, Mohammed F, Farouk A, Hatekayama C, Johnson K, Chow V, Ma S (2008) Genetic characterization of two 46,XX males without gonadal ambiguities. J. Assist. Reprod. Genet. 25:547–552. 2008.
24. Majzoub A, Arafa M, Starks C, Elbardisi H, Said SA, Sbanegh Jr E (2017) 46, XX karyotype during male fertility evaluation; case series and literature view. Asian Journal of Andrology. 19: 168-172.
25. Ucan B, Ozbek M, Topaloglu O, Yesilyurt A, Gungunes A, Demirci T, Delibasi T (2013) 46, XX Male Syndrome. Turk Jem, 17: 46-8.
26. Draganescu DD, Militaru M, Trifa A (2015) A case of 46, XX testicular disorder of sex development: clinical, molecular and cytogenetic studies. Acta Endocrinologica (Buc), XI (2): 233-239.

