Case Report: A Woman 27 Year Old with Mosaic Turner Syndrome Associate Hypogonadotropic Hypogonadism

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ABSTRACT

Background: Turner syndrome is a chromosomal abnormality found in phenotypically women who have one intact X chromosome and the absence of second sex chromosomes.

Case: The patient is a 27-year-old Javanese girl. At the age of 14 years, she came to the gynecology clinic with chief complaints of amenorrhea and then given cycloprogynova by the physician, the complaint improved but menstruation did not appear in the following month did not return to the gynecologist for evaluation. At the age of 26, she returned to the gynecologist and then was given medicine to stimulate menstruation and referred to an internist-endocrinologist because of a suspected hypothyroid. Then a few months later the patient returned to the gynecologist and then examined hormones, ultrasound, and karyotyping for evaluation as well as establishing the diagnosis. FT4 hormone examination results 0.87 ng / dl, TSHs 0.708 Uiu / mL, T3 (Total) 0.49 ng / mL, FSH 2.38 Miu / mL, LH 1.3 Miu / mL, prolactin 14.7 ng / ml, progesterone <0.10 ng / ml, estradiol <5 ng / ml indicates hypogonadotropic hypogonadism with hypothyroidism. Ultrasound results showed hypoplasia with uterine axis measuring 2.27 x 2.09 cm. Karyotyping result with 45x / 46xx indicate mosaic turner syndrome. Patients were given progestin, estero and also thyrax for hormone replacement therapy.

Discussion: Turner syndrome with hypogonadotropic hypogonadism is a rare variation of the turner syndrome. The definite cause is still uncertain. Some cases are usually accompanied by other hormone disorders such as thyroid and growth hormone.

Conclusion: A 27-year-old woman with hypgonadotrophic hypgonadism associated with mosaic turner syndrome. The diagnosis is done by history taking, hormone examination, imaging, and karyotyping. treatment given progestin, estrogen, and thyrax.

Keywords: Hygonadotropic, Hypogonadism, Turner Syndrome

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INTRODUCTION

Turner syndrome (TS) occurs in 25-50 per 100,000 women with clinical symptoms that involves multiple organs through all stages of life as well as requiring a multidisciplinary approach to care.\(^1\) Turner syndrome is a chromosomal abnormality found in phenotypically women who have one intact X chromosome and the absence of second sex chromosomes. Turner syndrome is related to one or more clinical manifestations.\(^2\)

Clinical manifestations of TS can be in the form of failure of linear growth, ovaries insufficiency (puberty delay), early sensorineural hearing loss, inborn, skeletal, digital cardiovascular and kidney anomalies, certain nerve development profile, and other existing constellation disorders more common in TS, including hypothyroidism and celiac disease.\(^3,4\) To make a definitive diagnosis for Turner Syndrome, karyotyping examination is assigned to the patients. TS genetic background varies greatly. The most common karyotypes are 45, X, karyotypes with isochromosomes X (i (Xq) or i (Xp)), mosaic karyotype 45, X / 46XX, and karyotypes containing the entire Y or its chromosome part. Five karyotypes of TS mosaics occur in around 30% of all patients with TS. The absence of puberty and primary amenorrhea occurs in most individuals with TS, due to accelerated oocyte loss in the ovaries 45, X, leaving several follicles in the form of fibrous at birth, these symptoms are often the first reason patients with TS come to the physician. In this case we report a 27 year old woman with mosaic TS and hipogonadotropic hypogonadism.

CASE

A 27-year-old woman was referred to the Department of Biology Medicine for karyotyping. At the age of 14, the patient went to the gynecologist because she had not had her menstrual cycle. She was performed an ultrasound examination and given cycloprogynova hormonal drugs for one month. During one month of medication the patient stated that she menstruated for 3 days but stopped experiencing menstruation again after the drug ran out and the patient did not visit the doctor. According to the patient, she did not visit the gynecologist because she had to enter the boarding school since graduating from junior high school. After graduating from high school, she returned to the gynecologist and had a laboratory examination and was declared normal. She was given another hormonal medication for one month and the patient had her menstruation, but in the following month when the patient did not consume the drug, the patient did not menstruate again. Then the gynecologist referred her to endocrinology subspecialty and took blood for endocrine examination with the following results (Table 1). The internist gave the thyroid hormone drug, Thyroxin, because the results of the patient's blood examination showed hypothyroidism. Then the patient was referred back to the gynecologist. At the physical examination she looked smaller than her age with height 145 cm and weight 42 kg, BMI: 20.47 kg/m\(^2\), and normal eye, ear, nose, and throat examination. Examination of the neck did not reveal a webbed neck. Her breast was tanner 2 with hyperpigmented areola. Examination of the hair on the armpits and outside genitalia did not show any fine hair. Examination of the abdomen and thorax was
normal and reproductive organs ultrasound revealed undeveloped ovaries and uterine hypoplasia with uterine axis measuring 2.27 x 2.09 cm (Figure 1). Gynecologist advised her to do a karyotyping examination. Karyotyping examination result was 45x/46xx (Figure 2).

Table 1: The Result of Hormone Examination

| Hormone     | Result  | References                                      |
|-------------|---------|------------------------------------------------|
| FT4         | 0.87 ng/dl | 0.93-1.71 (age > 19 years old)               |
| TSHs        | 0.708 Uiu/mL | 0.270-4.200 (age > 19 years old)            |
| T3 (Total)  | 0.49 ng/mL  | 0.79-2.05 (age > 19 years old)              |
| FSH         | 2.38 Miu/mL  | Folicular Phase: 6.9-12.5                    |
|             |          | Ovulation Phase: 12.3-21.5                   |
|             |          | Luteal Phase: 3.6-7.7                       |
|             |          | Postmenopause: 67.0-134.8                   |
| LH          | 1.3 Miu/mL | Folicular Phase: 2.4-12.6                    |
|             |          | Ovulation Phase: 14.0-95.6                   |
|             |          | Luteal Phase: 1.0-11.4                      |
|             |          | Postmenopause: 7.7-58.5                    |
| Prolactin   | 14.7 ng/ml | 4.79-23.3 (Woman, not pregnant)             |
| Progesteron | < 0.10 ng/ml | Folicular Phase: < 1.40                |
|             |          | Luteal Phase: 3.34-25.56                    |
|             |          | MidLuteal Phase: 4.44-28.03                 |
|             |          | Postmenopause: < 0.73                      |
| Estradiol   | < 5 ng/ml | Folicular Phase: 12.5-166                   |

DISCUSSION

Similar to TS (Turner Syndrome) patients in common, the chief complaint of TS patients come to the doctor is menstrual disorders. Most often is primary amenorrhea. In this case too, the patient comes to the doctor with menstrual disorders. In addition, short stature and absence of secondary sex characteristics which usually found in TS patients is also found in this patient. Other symptoms such as webbed neck, heart, eye, sensorineural disorders from physical examination were not found clearly in this patient.

Menstruation in women basically depends on the hormonal cycle that is regulated by the hypothalamus-pituitary-ovary axis mechanism. Hormones that play a large role such as estrogen and progesterone are produced via the hypothalamus-pituitary-ovary axis mechanism. The mechanism of the hypothalamus-pituitary-ovary axis in TS patients is the same as for women in general. In many cases of TS, low estrogen levels, due to undeveloped gonads, will give negative feedback to the
hypothalamus to stimulate more estrogen production so that there will be an increase in FSH and LH. Usually TS patients with ovary depletion show elevated levels of FSH and LH but low estrogen and progesterone levels. But interestingly in this case the patient showed low levels of FSH and LH. TS with hypogonatropic hypogonadism is not commonly found. In the literature there are only a few reported cases of TS with hypogonadotropic hypogonadism. The first case was a girl with thalassemia major and pituitary insufficiency attributed to haemotochrosis, the second and third were arachnoidocele with autoimmune disease and the last one was co-existing with immunodeficiency process.

Some literature report that TS with this condition is usually caused by the presence of a hypophytyuitarism concomitant factor. TS with suspicion of this factor has been reported by Esfthatidaou and Tsatsoulis, female patients aged 30 years was reported with GH deficiency, Thyrothrophin and sex steroids. TS with GH deficiency is very rare. the main cause of short stature in TS is not the result of GH deficiency but rather caused by haploinsufficiency of the short-bodied homeobox gene located on the short arm of the X chromosome (SHOX), an activator of transcription in osteogenic cell lines. The SHOX gene is located in the X chromosome region that escapes X inactivation. When SHOX haploinsufficiency occurs, there is decreased proliferation and differentiation of chondrocytes in the growth plate, leading to not only short stature but also bone deformities.

In this patient an MRI was performed in a subsequent evaluation and hypoplastic results in pituitary and ectopic localization of ectopic tuber cinerum. Reports with similar suspicions have also been reported by Gallichiou et al. Female patients aged 12 years were reported to have GnRH, TRH, and GH deficiency. In a further evaluation this patient had a CT scan and an empty sella turcica was obtained. In both cases with panhypophytyuitarism, the decrease in hormones both GnRH, GH, and TRH was caused by pituitary that did not develop. Closely possible in our case this is also true and imaging is needed in the pituitary.

TS is often associated with hypothyroid conditions and GH deficiency, but not always in all cases will be found hypogonadotropic hypogonadism as reported in this case. In this case the patient was diagnosed with a subclinical hypothroid. Livadas et al reported the incidence of TS with hypothyroidism in 1-40% of all TS cases, but in some cases there is also hyperthyroidism as much as 2-4% in TS. TS is also frequently associated with autoimmune hypothyroidism. The same thing was stated by Monzani et al and Mansoury et al. They state that one of the etiologies of the subclinical hypothyroidism is often related to genetic negligence such as turner syndrome and such conditions must be evaluated periodically for monitoring.

The correlation of thyroid autoimmunity with the type of karyotype abnormality does not show a persistent trend. Some theories suggest that primarily caused by thyroid amunity (hypothyroidism or hyperthyroidism) is more frequently encountered in girls with TS and especially in girls with Isochromosome Xq. In addition, the involvement of estrogen deficiency is also suspected of being one of the factors causing thyroid deficiency other than theories, The reason for predilection of the thyroid gland and the skin as a target of autoimmunity in patients with TS is not apparent but should be relevant to the general
observation of close correlation between thyroid autoimmunity and female gender. The proposed theory is that genes hindering on X chromosome are related to susceptibility to Hashimoto’s thyroiditis.\textsuperscript{16,17} However, linkage analysis have not verified this concept.\textsuperscript{18}

In the course of the disease it is important to consider whether or not hormone replacement is given.\textsuperscript{15} In this case For overcome clinical symptoms that occur, given hormone replacement therapy in accordance with the theory. It is recommended that women with TS should receive estrogen and progestin, which have a long-term effect on puberty, fertility, metabolism, and psychological functioning. Approximately 90\% of TS girls and women require HT to initiate, progress, and maintain puberty symptoms.\textsuperscript{15} Other hormone deficiencies can also be given as in the case of thyroid deficiency.\textsuperscript{19} In this case patients get progestin, esthero and also thyrax for hormone replacement therapy.

**CONCLUSION**

A 27 year-old woman with hypgonadotrophic hypgonadism associated with mosaic turner syndrome. The diagnosis of this disease includes a history of symptoms and signs that the patient complains about, then confirmed by laboratory tests such as hormones and imaging such as ultrasound. Karyotyping examination is highly recommended to confirm the patient's genotype. Therapy that can be given to these patients is progestin, esthero and tirax for hormone replacement therapy. The prognosis of this disease is relatively good. However, there will be many complications in the future that will affect the patient's quality of life.

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