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(CASE REPORT)

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Spontaneous Menarche in 45, X/47, XXX Mosaicism

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Abstract

Backgrounds: Turner syndrome (TS) also called monosomy X or Ulrich, is a congenital disorder caused by one intact X chromosome and the absence of second sex chromosomes. Only females are affected by Turner syndrome, characterized by abnormalities affecting the X chromosomes. Its incidence about 2.5-5.5 per 10,000 live births of girls. Mosaic 47, XXX karyotype is found in 3%-4% of TS patients.

Objective: To describe clinical manifestation and examination aspects of mosaicism turner syndrome.

Case presentation: An 18-years-old girl came with complaint short stature. This complaint has been noticed since the patient was in elementary school. The patient's parents initiated to have their child checked by pediatric endocrinologist when the patient was 6 years old. The patient was diagnosed with Turner syndrome from the result of chromosomal examination. The patient was given growth hormone by pediatrician with unknown dosage for approximately 1.5 years but the patient has never returned to control. During that period of time, her breast developed when she was 11 years old and the patient had menstruation at the age of 14 but the menstrual cycle was irregular. Physical examination showed the patient with short stature, low hairline, shield-shaped chest and right elbow deformity. The Sexual Maturity Rating score was M4P4. Her anthropometric status was overweight and short stature with height for age < P3rd. The patient's bone age was equivalent with child age 17-years-old. Karyotype examination with G-banding technique, the chromosomes from 40 cells have been studied and the number of chromosomes in each cell studied is mos 47, XXX[30]/45, X[10]. Ultrasonography examination showed the uterus anteflexed below normal size, the right ovary appears below normal size, and the left ovary is not visible.

Conclusion: An 18-year-old girl with mosaic Turner syndrome. The diagnosis is established by history taking, physical examination, hormone examination, imaging and karyotyping. Patient was treated with growth hormone.

Keywords: Mosaicism; Turner syndrome; Girl; Karyotype; Chromosomes

1. Introduction

Turner syndrome (TS) also called monosomy X or Ulrich - Turner is a congenital disorder caused by part or all of the X chromosome is missing. It was introduced by Turner in 1938, the syndrome occurs in women with clilnical manifestation short stature, gonadal dysgenesis, major and minor congenital anomalies caused by abnormalities in the sex chromosomes[1]. Only females are affected by Turner syndrome, which is characterized by abnormalities affecting the X chromosomes. Its incidence is 2.5-5.5 per 10,000 live births of girls. The incidence in Japan is 7-21 per 10,000 live births for girls. The incidence is much higher because TS is one of four spontaneous abortions caused by chromosomal anomalies that have not been clinically diagnosed. Incomplete X chromosomes (45, XO), generally occurs sporadically and about 8-16% of them are mosaics. Parents have nothing to do with the age of incidence of TS[2,3]. More than half of Turner Syndrome is undiagnosed until the age of 12-14 years, because secondary sex characteristics have not

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develop[4]. 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[5].

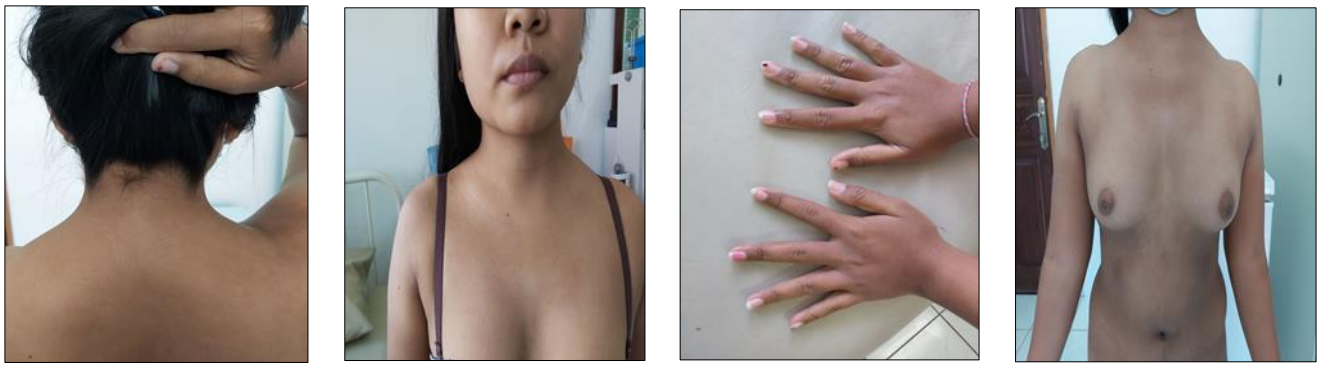
Clinical manifestations of TS including failure of linear growth, ovaries insufficiency (puberty delay), early sensory neural hearing loss, skeletal, digital, cardiovascular, kidney and neuro developmental anomalies and other existing constellation disorders more common in TS, including hypothyroidism and celiac disease[5,6]. Prenatal diagnosis can be made from ultrasonography (USG) finding, amniocentesis for examination of human chorionic gonadotropin (HCG) level, cytogenetics and examination of maternal serum HCG. Postnatal diagnosis can be established from physical characteristics and karyotype examination[7]. The management of patients with TS requires the cooperation of several branches of medical science since the patient is diagnosed during pregnancy, postpartum, child development and psychological development[1,4]. Recent studies indicate that the growth deficiency in Turner Syndrome can be corrected by injections of 'human growth hormone' before growth is complete. Oral hormone replacement will promote pubertal development. Genetic and reproductive counseling is needed for psychological effects. Sometimes surgical therapy is needed to correct defects in the affected organs[1]. In this case we report an 18 years old girl with mosaic TS. We report a case of 18 years old girl with overweight and short stature. She is a 45,X/47,XXX mosaic.

2. Case report

An 18 years old girl was referred to Pediatric Endocrinology policlinic Sanglah Hospital from the outpatient of internal medicine with diagnosis Turner Syndrome. Previously, the patient felt that her height was not like her peers. Patients feel short when compared to friends, or other family members. This complaint has been noticed since the patient was in elementary school. The patient's parents initiated consultation to pediatric endocrinologist when the patient was 6 years old. During that time, several examinations were carried out including bone age, thyroid hormone levels, and chromosomal examination. The patient was diagnosed with Turner syndrome at the age of 6 years from the results of chromosomal examination. The patient was regularly monitored by Pediatric Endocrinologist and received growth hormone injections for 1.5 years with unknown dosage after that, the patient has never returned to control. It is said that her breasts have developed at the age of 11 years and had menstruation at the age of 14 years. It is also said that her menstrual cycle is irregular, sometimes every 3 or 4 months. Then the patient returned to Sanglah hospital for control. The first day of last menstruation was December 12th, 2021 for 4 days. There was no other complaint at the time.

The patient is the second child of 2 siblings, the patient's sister is said to be healthy, is said to has short stature too, but is currently married and has 1 child. No family members suffer the same disease. History of liver disease, kidney disease, high blood pressure, cancer, tuberculosis, or other diseases in the family were denied. The anthropometric status of patient, her bodyweight was 40 kg, bodyheight was 140 cm and the ideal bodyweight was 35 kg. In the CDC 2-20 years curve stature for height for age data showed <P3rd, weight for height showed P50-75. The patient's BMI was 20.4 kg/m^2. BMI/age range P25-50. Nutritional status was 112%. The mother’s height was 155 cm. Father's height was 165 cm. Genetic potential height was 145 cm to 162 cm. Mid Parenteral Height (MPH) 153.5 cm. Patient was concluded with overweight and short stature.

The general condition of the patient was mild. Physical examination showed short stature and normocephalic head (head circumference 50 cm), with low hairline at the back of the neck, and no extra folds of the skin. There were no facial features (dysmorphic features) and certain syndrome facies. From the eye examination, the conjunctiva was not pale, not hyperemic, no discharge, the sclera was not icteric, the pupil was isochoric, positive light reflex, and no edema, no buckling, no conjunctival deviation or strabismus. From the ENT examination, there was no discharge in the ear, no low set ear. There was secret in nose and no nostril breathing. From the examination of the throat, the pharynx was not hyperemic, both tonsils were T1 in size and not hyperemic. There was no cyanosis of tongue. Dry lip mucosa, no cyanosis. Jugular venous pressure was not evaluated, gland enlargement was absent, and nuchal rigidity was absent. On examination, the thorax looks symmetrical, shield shape chest, without retraction. Normal and regular heart sounds, no murmur. Vesicular breath sounds in both lung fields, no rales nor wheezing. No abdominal distension, no tenderness, rapid return of turgor, no ascites, no palpable liver, no spleen, no abdominal mass. Extremities palpable warm, no edema, capillary refill time is less than 2 seconds, and no small fingernails. There is elbow deformity of the right hand. There was no cyanosis of the skin. On genital examination, there were no abnormalities. The Sexual Maturity Rating score was M4P4.



A B C D

Figure 1 (A) low hairline (B) no fold of skin (C) no small fingernails (D) shield-shaped chest and right elbow deformity

Laboratory examination revealed 1.28 ng/dL of free thyroxine (normal range: 0.8 to 1.8), 1.67 μIU/mL of thyroid-stimulating hormone (TSH) (normal range: 0.5 to 5), <0.20 mIU/mL of luteinizing hormone (LH) (normal range: 0.02 to 4.7), 2.22 mIU/mL of follicle stimulating hormone (FSH) (normal range: 0 to 10.8), 18.09 pg/mL of estradiol (normal range: 10 to 24). BUN and creatinine test is 9.62 and 0.52 mg/dL. Liver function tests were SGOT 42 U/L and SGPT 51 U/L.

ECG examination shows normal sinus rhythm, normal axis, no LVH and RVH and no ST-segment changes. The bone age was found in accordance with the description of a 17-years-old girl's bone age.

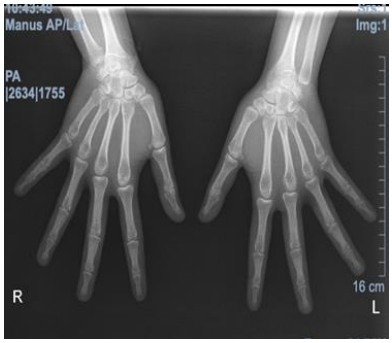


Figure 2 Bone age examination showed bones in accordance with the description of 17-year-old girl

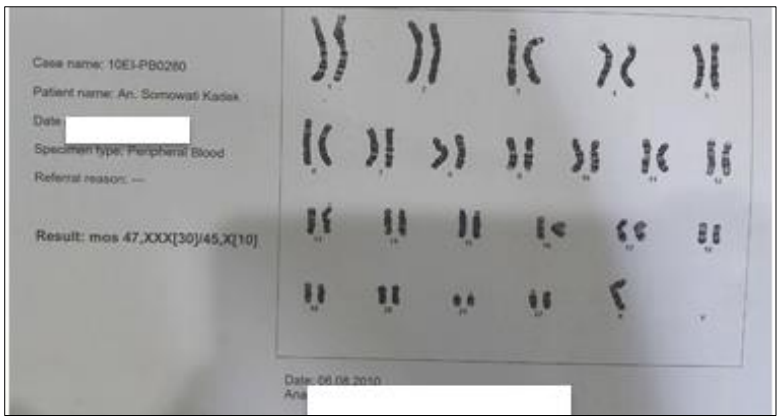


Figure 3 Karyotype examination resulted the number of chromosomes in each cell studied is mos 47, XXX[30]/45, X[10]

Karyotype examination with the G-banding technique, the chromosomes from 40 cells have been studied and the number of chromosomes in each cell studied is mos 47, XXX[30]/45, X[10].

The patient was consulted to Obstetrics and Gynecology Department and performed USG examination. The USG examination showed ante flexy uterus, below normal size, the right ovary appears below normal size, and the left ovary is not visible.

3. Discussion

Turner syndrome (TS) also called monosomy X or Ulrich - Turner is a congenital disorder caused by missing of partial or all of the X chromosome. The clinical symptoms of Turner Syndrome (Bonnevie-Urlich Syndrome) was established based on clinical examination of the presence of Turner stigmata, including short stature (BH: 130 cm), a shield-like chest with wide distance nipples, failure of secondary sex growth, *cubitus vagus* arm and confirmed by karyotyping examination (45, X). Early diagnosis, in this case, could be done because the patient arrived early at the age of 6. Indeed, in this syndrome, the diagnosis is generally made after the age of 12-14 years, when secondary sexual development fails[5]. In this case, patient was diagnosed with Turner syndrome at the age of 6 years from the results of chromosomal examination.

Publications on the subject allow establishing some major differences between 47XXX cell-line females, those with 45X/ 46XX, and those with 45X only[6]. In TS females with sex chromosome aneuploidy, streak gonads, edema at birth, and short stature are generally recorded. Many infants with postnatal edema still show signs of prenatal edema, i.e. webbed neck and anteverted ears[7]. Similar findings (neonatal edema, slightly webbed neck, abnormal growth) were present in the 45X/47XXX case presented in this work, which may be related to quantitative dominance of the 45X cell line in both obtained karyotypes[6]. From the phenotypic perspective, individuals with the 45X/47XXX mosaic karyotype do not necessarily show the characteristic signs of TS, because of the presence of the 47XXX line[6]. The triple X syndrome itself often remains undiagnosed, since in the process of lionization third X chromosome became inactive and does not have large impact on phenotype. If symptomatic, 47XXX syndrome may resulted tall stature, microcephaly, epicanthal folds, language learning disabilities, or muscular dystonia[8]. It is interesting that in the described case, the asymmetric growth has been observed and surgically corrected later in life. It can be hypothesized that hemihypotrophia was related to different distribution of cell lines in the body, and the site with a higher percent of 47XXX was growing faster than the monosomic line[9]. According to the available data, it is a rare finding in mosaic TS karyo/type, while 0–5% of the affected adults manifest skeletal anomalies[9,10].

Short stature is one of the problems with Turner Syndrome. It is said that GH therapy should be given when his height falls below the 5th percentile of normal growth curve, usually between the ages of 2-5 years. In this case, the patient came at the age of 6 years. There is still hope in these patients to increase body height, although maximum results will not be obtained. The growth rate should be monitored every 6 months. Therapy does not respond if the growth rate is 2 cm in 6 months or 4 cm in a year. Monitoring of blood sugar, lipid profile, thyroid function and IGF-1 are necessary to be performed annually and bone mineral density (BMD) at puberty, growth hormone therapy can be given until the bone age (bone age) is 14 years or unresponsive. The final result of height without therapy was 140.8±5 cm, with growth hormone therapy alone was 147.9±7.2 cm, and with growth hormone-estrogen therapy was 149.3± 6.6 cm[12]. In this case, patient had growth hormone therapy. Children with growth hormone therapy will have good outcome. Jung Min et al., concluded that GH treatment at early age is effective in improving the final height SDS and height SDS gain in TS patients. Therefore, GH administration at early age is important for final height again[13]. It is suitable for our case.

TS is typically associated with gonadal dysgenesis and infertility, which are its primary features. The gonadal failure is effect of accelerated follicular loss in early childhood and is typical in TS individuals with monosomy[15]. It is evident that XXX cell presence results in likelihood of residual ovarian function[6,8,10]. It is also correlated with spontaneous menarche, which is more common in XXX cell individuals than those with 45X (70% and 11%, respectively)[14]. 45X/47XXX females present with various degrees of ovarian function, starting from normal to absent with mono or bilateral streak gonads[6,7,10]. Gradual loss of the X chromosome with age may partially explain premature ovarian failure (POF). Also, in the presented case we have observed a transition from eumenorrhea to secondary amenorrhea related to POF, which has been confirmed with FSH elevation, anti mullerian hormone (AMH) decrease, and ultrasound imaging[16]. The patient presented with short stature but had no congenital anomalies and developed spontaneous puberty and menarche. Past history of growth hormone treatment, her near final adult height reached the target height range. Total 3–4% of all TS individuals have mosaic for the 47XXX cell line, which makes them prone to spontaneous menarche and more fertile, as compared to 45X[6]. Natural pregnancy in TS is not common but is most likely to occur in its mosaic karyotype variety. TS females who manage to conceive are at increased risk of miscarriage, stillbirth, congenital malformation, or aneuploidy of their offspring[6,11].

Previous studies of young 45, X/47, XXX mosaicism patient puberty and fertility features indicated that their phenotype is less severe than that of common TS patients[16,17]. In this case and according to previous reports, 45,X/47,XXX mosaic TS has mild clinical manifestations than those of classic TS and patients often retain sexual function until early adulthood. However, the risk of premature ovarian insufficiency (POI) is higher than that in the general population, which needs monitoring of gonadal function and careful counseling for family planning. 45,X/47,XXX mosaic TS is a very rare genotype. Thus, the exact clinical course cannot be predicted. More research is needed to provide specific guidelines to ensure proper approach for growth, pubertal development, and fertility in TS with 45X/47,XXX karyotypes.

This patient has a 1 : 3 ratio of 45, X : 47, and XXX karyotypes in the cells examined from her peripheral blood smear. However, this does not necessarily reflect the distribution of cells throughout the organ systems of her body. Moreover, most patients assessed for Turner syndrome have only been karyotyped from one tissue, so we do not know which lines dominate in which organs. Researchers at USC Medical Center reported the case of a patient with short stature whose buccal smear showed 45, X/46, XX/47, XXX in a 67/123/10 ratio, whose peripheral leukocyte culture showed 45, X/47, XXX in a 1/1 ratio, and whose skin fibroblast culture showed 45, X/47, XXX in a 5/19 ratio[18,19]. They confirmed a previous assertion that the proportions of chromosomally different cell lines have little value for phenotype prediction because the chromosome makeup is so varied depending on the sample tissue. However, they presumed that the 47, XXX line was dominant because of the minor Turner syndrome stigmata. Yet, the 45, X line determined her height.

The prognosis of patients with Turner Syndrome is highly dependent on the age when first recognized. In this case, this patient seeks help at the age of 6 years old. Because it's diagnosed early, we can expect better prognosis. In terms of sexual function, with the development of normal external genitalia and the presence of vagina, sexual function is expected to be like other normal women. From reproductive perspective, this patient has relative small-sized uterus and the left ovarium is not visible. The treatment option for infertile Turner Syndrome women is in vivo fertilization with egg donors. Some health facilities can achieve pregnancy at rate 50-60% with this technique. However, there is hope for these sufferers as more than 50 natural pregnancies have been reported in women with Turner Syndrome[3].

Overall, making predictions regarding what the future has in store for these mosaic girls is nebulous. For prenatal diagnosis, parents of 45, X/47, XXX girls should be counseled for the possibility of full Turner symptoms but with optimism for better outcome. Intellectual impairment is reduced compared to 45, X Turner syndrome, which is an important concern for parents who may be considering selective termination[6]. Future fertility also cannot be guaranteed but can be successful in most 45, X/47, and XXX women. An accurate karyotype diagnosis is vital to establish possible impairments typical of certain karyotypes and TS related mosaicism. As the consequences of late diagnosis of the condition are severe and lifelong, the importance of timely and accurate diagnosis must be emphasized[19]. One of the most important hopes for this patient is to create sense of self-confidence and self-esteem as a woman who lives in social environment. The current hope to restore physical posture and reproductive function needs to be explained by reproductive counseling.

4. Conclusion

An 18-years-old girl presented to the Pediatric Endocrine outpatient clinic of Sanglah Hospital, with complaint of short stature. This complaint has been noticed since the patient was in elementary school. The patient's parents initiated consultation to pediatric endocrinologist when the patient was 6 years old. The patient was diagnosed with Turner syndrome at the age of 6 years from the results of chromosomal examination. The therapy that has been given is growth hormone with an unknown dosage for approximately 1.5 years but after that, the patient never returned to control. Finally, her breasts appeared when she was 11 years old, and had menstruation at the age of 14. However, the menstrual cycle is irregular, sometimes every 3 or 4 months. Physical examination showed short stature, low hairline, shield-shaped thorax. The Sexual Maturity Rating score was M4P4. From the anthropometric status, patients with overweight and short stature with height/age showed <P3. Radiology examination showed that the patient's bone age was equivalent to that of a 17-years-old child. On karyotype examination with the G-banding technique, the chromosomes from 40 cells have been studied and the number of chromosomes in each cell studied is mos 47, XXX[30]/45, X. USG examination showed the anteflexed uterus, below normal size, the right ovary appears below normal size, and the left ovary is not visible.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participant included in the report.

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