CASE REPORT

Bali Medical Journal (*Bali MedJ*) 2022, Volume 11, Number 1: 466-470
P-ISSN.2089-1180, E-ISSN: 2302-2914

Turner syndrome and tuberculosis in adolescent: a case report

Nyoman Titamarita Trisnawan[1*], Florencia Christina Sindhu[1], Peter Prayogo Hsieh[1], Arya Putri Ratnasari[1], Alberto Afrian[1], Ancelia Limantara[1], Han's Christian[1], Made Ratna Dewi[1], I Wayan Bikin Suryawan[1]

[1]Department of Child Health, Wangaya General Hospital, Denpasar, Bali, Indonesia;

*Corresponding author:
Nyoman Titamarita Trisnawan;
Department of Child Health, Wangaya General Hospital, Denpasar, Bali, Indonesia;
dk6230er@gmail.com

Received: 2022-02-26
Accepted: 2022-04-25
Published: 2022-04-30

ABSTRACT

Background: Turner syndrome is characterized by abnormality of one X chromosome. Those with Turner syndrome are at risk of developing tuberculosis infection due to decreased immune function.

Case: A 17-year-old girl came with complaints of short stature, amenorrhea, and no signs of secondary sexual growth. She also felt weak. On physical examinations, she weighed 24 kg, and her height was 119 cm. Her conjunctiva looked pale. She had a low set hairline, small mandible, short 4th metacarpal, and wide-spaced nipple. Her breast and genitalia did not grow (1st stage of Tanner classification). There was a lesion between her breasts. Laboratory results showed Hemoglobin 7 g/dL, MCV 62,6 fL, MCH 18,2 pg, MCHC 29 g/L, FSH >170 IU/L, LH 95,3 IU/L, Estradiol 11 pg/mL, Iron Ferrozine 7 mg/dL, TIBC 186 µg/dL, and Ferritin 50 ng/mL. Her Mantoux test showed induration with a diameter of 20-23 mm, and the Xpert MTB-RIF test showed low detection of MTB. Her bone age was appropriate for a 13-year-old girl. Histopathology test of her lesion showed chronic granulomatous inflammation. Her chromosome analysis showed Mos 45,X(56)/46,XX(44). She was diagnosed with Turner syndrome and tuberculosis. She received Progynova® 2 mg every 24 hours for 21 days, stopped for 10 days, and continued again for 21 days. She also got anti-tuberculosis drugs (pediatric regime).

Conclusion: The clinical spectrums of Turner syndrome vary widely. Decreased immune function in Turner syndrome can lead to infections such as tuberculosis. Early diagnosis and treatment can prevent further morbidity.

Keywords: *adolescent, clinical profiles, tuberculosis, turner syndrome*.
Cite This Article: Trisnawan, N.T., Sindhu, F.C., Hsieh, P.P., Ratnasari, A.P., Afrian, A., Limantara, A., Christian, H., Dewi, M.R., Suryawan, I.W.B. 2022. Turner syndrome and tuberculosis in adolescent: a case report. *Bali Medical Journal* 11(1): 466-470. DOI: 10.15562/bmj.v11i1.3243

INTRODUCTION

Turner syndrome is one of the most common chromosomal disorders characterized by the loss of one X chromosome.[1] Based on karyotyping examination, there are two X chromosome abnormalities in Turner syndrome, classic and mosaic form.[2] The classic form is identified as 45,X and the mosaic form as a structural abnormality on the X chromosome, such as 45,X/46,XX or 45,X/47,XXX.[2] The incidence of Turner syndrome is 1:2,000-1:2,500 live births in girls regardless of any ethnic background.[1,2] Clinical symptoms of Turner syndrome have a broad spectrum, ranging from disorders of growth, reproductive system, autoimmunity, and abnormalities of the cardiovascular and endocrine system.[2,3] Any other abnormalities that could be found are a webbed neck, widely spaced nipples, cubitus valgus deformity, and low posterior hairline.[4] These clinical features tend to influence the patient's age at diagnosis.[4]

Tuberculosis infection is one of the most common infectious diseases, especially in developing countries.[5] There are 10 million people infected by this disease every year, and 1.6 million die from it.[5] In Indonesia, the data from 2018 showed the incidence of tuberculosis was 316/1.000 people, and the mortality rate was 40/100.000 people.[6] It's estimated that there are 500.000 new cases every year here in Indonesia.[6] Children with decreased immune function are at risk of developing tuberculosis infection. Turner syndrome is thought to be one of the causes of the alternated immune system due to reduced numbers of circulating T and B lymphocytes, which are important to combat *M.tuberculosis*.[7]

Achieving good quality of life is the main goal for the patient, so the diagnosis and treatment must be made as early as possible.[3,8] In developing countries, delayed diagnosis of Turner syndrome appears to be more common.[3] This case report was written with the aim of providing a description and clinical pictures of Turner syndrome and tuberculosis in adolescents.

CASE

A 17-year and 10-months old girl came to the polyclinic complaining of a shorter height than her peers, no menstruation yet, and no signs of secondary sexual growth. The patient also complains of weakness, fatigue, and lethargy. In addition, there have been purulent wounds on the chest and right hand since approximately two years ago. The patient had a history of surgical scars on the chest one year ago. The results of the pathological examination of the wound at that time concluded that

Figure 1. Low set hairline

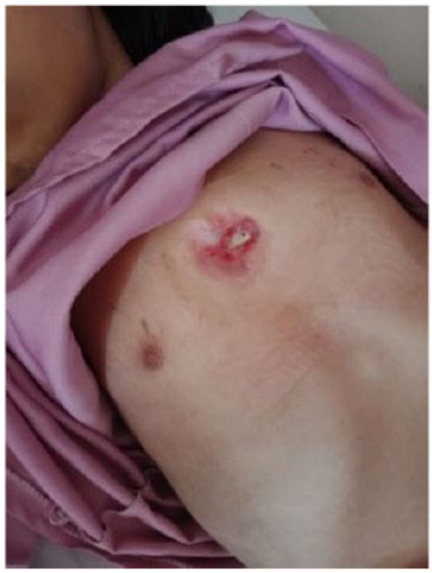

Figure 2. Wide nipples space with chronic suppurative scar.

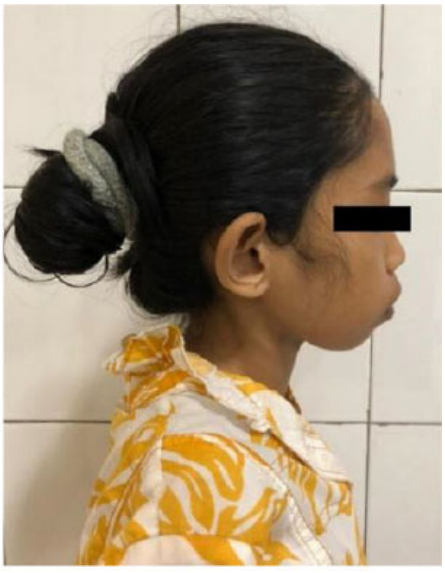

Figure 3. Small mandible appearance.

in the sternum region, there was a chronic suppurative granulomatous inflammation up to the hard bone tissue, and the tubercular process could be considered. The patient is the last child in her family. None of the other family members had the same complaints as the patient. The patient usually eats three times a day with one portion of rice, eggs, tofu, tempeh, fish, and vegetables.

On anthropometric examination, the body weight was 24 kg (weight/age <P5), height 119 cm (height/age <P5), weight/height (P50-75), the upper segment height was 64 cm, and the lower segment was 55 cm so that the A/B ratio was 1.16, and the ideal body weight is 22 kg. The nutritional status of children based on Waterlow is good nutrition (109%). The height of the mother is 151 cm, and the height of the father is 160 cm, so the genetic potential of the patient is 140.5-157.5 cm. Vital signs of the patient were examined with the result: blood pressure 90/60 mmHg, pulse 98×/minutes and regular, respiratory rate 20×/minutes and regular, temperature 36.5°C, and oxygen saturation 98% in room air. Normal head shape with low set hairline (Figure 1), eye conjunctiva is anemic, the lower chin looks small (micrognathia), surgical scars appear in the anterior thoracic region, breasts do not show any sign of secondary growth, the distance between two nipples are 14 cm (wide impression of nipples space). Examination of the heart, lungs, and abdomen were within normal limits. The upper arm appears to have cubitus valgus deformity, and there was a shortening of the fourth finger in the left hand. Genu varus deformity in limbs can be seen. On genital examination, the female genitalia was found with the labia majora covering the labia minora and no hair growth and pale skin. According to Tanner's classification, the breasts and genitals are still in stage 1.

Based on history taking and physical examination, the patient was suspected of having Turner syndrome, anemia, and tuberculosis infection. Therefore, we planned a further examination, and the results of the examination are listed in Table 1.

Based on the history taking, physical, and supporting examinations, a diagnosis of Turner syndrome, iron deficiency anemia, pulmonary and cutaneous tuberculosis, and good nutritional status can be established. Therefore, the patient received Progynova® 2 mg every 24 hours for 21 days, then stopped for 10 days, and continued again for 21 days. The regimen was planned to be repeated for the rest of her life. The patient also received drugs for tuberculosis infection: isoniazid 10 mg/kg/day, rifampin 10 mg/kg/day, pyrazinamide 15 mg/kg/day, and ethambutol 15 mg/kg/day. The regimen is planned to be given for 2 months (intensive phase), followed by isoniazid 10 mg/kg/day and rifampin

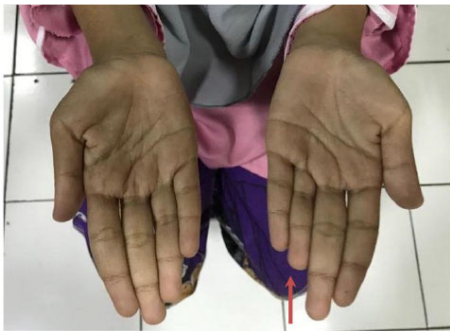

Figure 4. Shortening of fourth finger in the left hand.

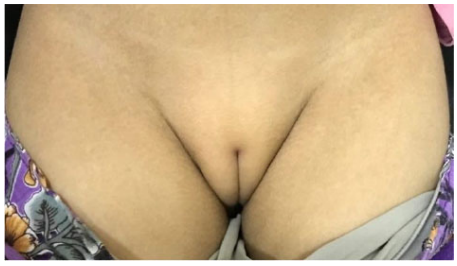

Figure 5. Tanner's 1 classification on genital appearance.

10 mg/kg/day for 4 months (advanced phase) according to the TB management guidelines from the Ministry of Health Republic of Indonesia. The patient also received vitamin B6 (Pyridoxine®) 10 mg every 24 hours to prevent the side effect of isoniazid, called peripheral neuritis. The patient was advised to visit the polyclinic regularly for check-up and monitor the side effects of anti-tuberculosis drugs.

Figure 6. Short stature and cubitus valgus deformity.

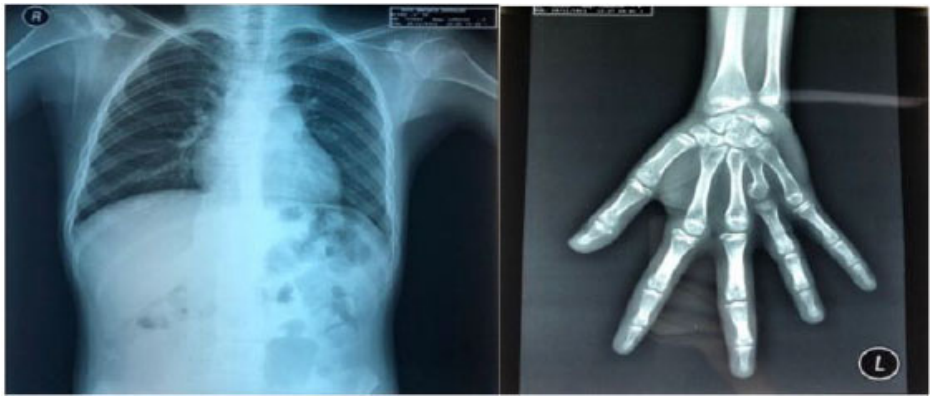

Figure 7. Chest X-Ray and Bone Age Examination.

DISCUSSION

Based on the age at diagnosis, the patient in this case report was late because she came at the end of the puberty period, which was 17 years and 10 months. Delayed diagnosis of Turner syndrome is more common in developing countries.[3] This result was in line with a study by Wonkam et al., which found that the average age of patients with Turner syndrome who came for treatment for the first time was 18.4 ± 2.8 years old.[9] The delay that occurred in the patient in this case report was probably due to a lack of knowledge and attention to children's growth and development because the patient came from a family with a low level of education and lives in a rural part of Indonesia.

Turner syndrome has a wide spectrum of signs and symptoms. The most common complaints are growth retardation and gonadal failure.[10] The short stature that occurs in Turner syndrome is caused by an insufficiency of the short-stature homeobox-containing gene on the X chromosome (SHOX) located at the end of the X chromosome.[11] Gonadal failure in Turner syndrome is caused by a partial deletion of the short arm of the X chromosome caused excessive oocyte cell death.[12] In accordance with the case report above, the patient came with a complaint of short stature as evidenced by the results of height for age examination (Height/Age) below P5 and confirmed by bone age examination, which showed bone age according to a woman aged 13 years old. Gonadal failure, which resulted in the absence of secondary sex signs in the patient, was proven by Tanner's classification of the breast and genitals of the patient still in stage 1, which was confirmed by laboratory results, increased FSH and LH levels and decreased in estradiol levels. After doing a karyotyping examination, the results showed mos 45,X(56)/46,XX(44). According to the study, the mosaic form most commonly associated with short stature and gonadal failure was 45,X/46,XX.[12] Renal abnormalities are also common in patients with Turner syndrome, where renal anomalies can be found in 30% of patients. Examination of kidney function can be used for early detection of kidney abnormalities in patients with Turner syndrome.[13] In addition to renal impairment, 10-30% of patients with Turner syndrome also have autoimmune thyroid disease.[14] For this reason, the patient in the case report above, underwent kidney function and thyroid function tests, and the results of the examination of both organs were within normal limits.

On physical examination, one or more dysmorphic features are often found in patients with Turner syndrome.[1] Some of these include high palate, low set ears, low posterior hairline, webbed neck, wide nipple space, small mandible, ptosis, nail dysplasia, cubitus valgus deformity, and shortening of the fourth metacarpal.[1,14,15] Bucerzan et al. conducted a study involving 45 patients with Turner syndrome.[16] In this study, it was found that 69% of correspondents had a low set posterior hairline, 67% had a shortened fourth metacarpal, 91% had a pectus excavatum, and 33% had a webbed neck.[16] Physical examination in the patient above revealed more than one dysmorphic feature, such as low set hairline, wide nipple space, cubitus valgus deformity, and shortening of the fourth metacarpal.

Because the patient complained about weakness, fatigue, and lethargy, a complete blood count was conducted, and the hemoglobin level was below normal with suspicion of iron deficiency anemia due to low levels of MCV, MCH, and MCHC. Then the peripheral blood smear and iron panels were examined. Examination of the peripheral blood smear gives the impression of suspicion towards iron deficiency anemia or anemia of chronic disease, which is then confirmed by the results of the iron panel examination, which gives a general appearance of iron deficiency.

Suspicion of the occurrence of tuberculosis (TB) infection in patients arises because the patient comes from a rural area with poor sanitation, where poverty and an environment with poor hygiene are risk factors for TB infection.[17] Therefore, the patient was also planned to undergo a chest X-ray examination, Mantoux tuberculin skin test, and rapid

Table 1. Laboratory and Radiographic Examination Results.

Inspection	Results
Full Blood	
Leukocytes	8.260/uL
Hemoglobin	7 g/dL
MCV	62.6 fL
MCH	18.2 pg
MCHC	29 g/L
Hematocrit	24.1%
Platelets	550.000/uL
Neutrophil/lymphocyte ratio	5.59
LED	20mm/hour
Endocrinology	
FSH	>170 mIU/mL
LH	95.3 mIU/mL
Estradiol	11 pg/mL
TSHs	0.2 mIU/mL
FT4	1.1 ng/dL
Blood Chemistry	
GDS	101 mg/dL
SGOT	8 U/L
SGPT	23 U/L
urea	18 mg/dL
Creatinine	0.4 mg/dL
Fe Panels	
Iron ferrozine	7 mg/dL
TIBC	186 g/dL
Ferritin	50 ng/mL
Radiology Inspection	**Result**
Thoracic plain photo	The heart and lungs do not show any abnormalities
Bone age	The impression is suitable for a 13-year-old woman, showing a shortening of the 4th finger metacarpal
Peripheral blood smear	RBC appears as hypochromic anisopoikilocytosis (normocytic, microcytic, pencil cells, teardrop cells)
Mantoux tuberculin skin test	Induration 20-23 mm
Molecular rapid test	(+)
Xpert MTB-RIF	MTB very low detection, RIF resistance (-)
PA scrapping ulcer	Suppurative granulomatous chronic inflammation
Chromosome analysis	Mos 45,X(56)/46,XX(44)

molecular test using Xpert MTB-RIF. Although the results of the chest X-ray showed no abnormalities, the Mantoux tuberculin skin test and molecular rapid Xpert MTB-RIF examination confirmed that the patient had a TB infection. In addition, the complaint of a wound on the patient's chest was suspected to be a clinical manifestation of cutaneous tuberculosis. The patient was then planned for histopathological examination, and the impression of chronic granulomatous suppurative inflammation was found. The presence of chronic granulomatous inflammation is one of the histopathological signs of cutaneous tuberculosis.[18] With A positive TB examination plus histopathological examination that leads to the characteristics of skin disorders due to tuberculosis, the diagnosis of cutaneous TB can be established.

Patients with Turner syndrome are associated with decreased immune function due to reduced numbers of circulating T and B lymphocytes.[7] Impaired function of T lymphocytes in patients with Turner syndrome is thought to be due to insufficiency of the UTX gene on the X chromosome.[7] Insufficiency of the UTX gene manifests as impaired differentiation of CD4+ T lymphocytes into T follicular helper (Tfh), which plays a role in B lymphocyte maturation.[7] This can explain a decrease in the number of T and B lymphocytes in the circulating blood of patients with Turner syndrome. As we know, T and B lymphocytes have a very significant role in the elimination of TB germs, and they play a role in producing cytokines that activate macrophages to eliminate TB germs.[17]

Short stature is the most common manifestation of Turner syndrome, and administration of growth hormone (GH) therapy can improve the final height of the patient by up to 5-8 cm and even up to 17 cm.[11,19] Growth hormone therapy is best given at 4-6 years of age or earlier if failure to thrive is found, in order to provide an adequate duration of therapy before puberty begins.[11] In addition, prolonged exposure to GH therapy will have a good long-term impact on fat metabolism and increase the number of red blood cells, as evidenced by a decrease in erythropoietin levels.[20] Although about 30% of Turner syndrome patients with mosaic karyotype may experience spontaneous puberty, hormone replacement therapy with estrogen/progesterone should be initiated immediately for sexual function maturation.[11] The regimen used is conjugated estrogen plus progestin for 10-12 days every month to induce menstruation and reduce the risk of endometrial hyperplasia and/or carcinoma.[1] The patient in the case report above received therapy with Progynova® 2 mg every 24 hours for 21 days, then stopped for 10 days and continued for 21 days. The regimen was planned to be repeated for the rest of her life. The patient did not receive GH therapy due to irrelevant function and cost constraints. In addition, because the patient also had cutaneous tuberculosis, the patient received anti-tuberculosis drugs: isoniazid 10 mg/kg/day, rifampin 10 mg/kg/day, pyrazinamide 15 mg/kg/day, and ethambutol 15 mg/kg/day. The regimen is planned to be given for 2 months

(intensive phase), followed by isoniazid 10 mg/kg/day and rifampin 10 mg/kg/day for 4 months (advanced phase) according to the TB management guidelines from the Ministry of Health Republic of Indonesia. The patient also received vitamin B6 10 mg every 24 hours to prevent the side effect of isoniazid called peripheral neuritis.[17] Prior to starting anti-tuberculosis drug therapy, the patient underwent liver function tests to ensure that there were no liver function abnormalities before starting the medication.

Turner syndrome in female patients that were diagnosed in early childhood can get maximum support from their family and environment, so the academic, education, social life, and physical appearance (height and sexual function) even are able to achieve a near-normal female.[21] Study by Cheng Lee et al. stated that late diagnosis and treatment after the median menarche age (13 years old), less likely the growth hormones treatment would be relevant and effective. In this patient, we only give the estradiol hormones without growth hormones.[21] The starting dose of estradiol for the patient with late-onset diagnosis is based on individual priority, whereas in this patient, due to sexual maturity stimulation.[21]

CONCLUSION

Turner syndrome has a very wide spectrum of symptoms. Decreased immune function in Turner syndrome can lead to multiple infectious diseases, one of which is Tuberculosis infection. Good recognition of the sign and symptoms of Turner syndrome can prevent delays in diagnosis, which can result in a decrease in the patient's quality of life. The earlier the diagnosis and treatment are, the better the quality of life that can be achieved by the patient.

CONFLICT OF INTEREST

There is no conflict of interest in the writing of this paper.

FUNDING

The author is responsible for funding this paper.

ETHICS IN PUBLICATION

The patient's parents have signed the informed consent and agreed that the medical data would be published in the form of case reports in medical scientific journals.

AUTHOR'S CONTRIBUTION

All authors contributed to writing this paper, starting from patient examination, data collection, and report writing.

REFERENCES

1. Batubara JRL, Utari A, Susanto R. Sindroma Turner. In: Batubara JRL, Parwoto BTAA, Pulungan AB, editors. Buku Ajar Endokrinologi Anak. 2nd ed. Jakarta: Badan Penerbit Ikatan Dokter Anak Indonesia; 2018. p. 40–4.
2. Cui X, Cui Y, Shi L, Luan J, Zhou X, Han J. A basic understanding of Turner syndrome: Incidence, complications, diagnosis, and treatment. Intractable Rare Dis Res. 2018;7(4):223–8. https://doi.org/10.5582/irdr.2017.01056
3. Kruszka P, Addissie YA, Tekendo-ngongang C, Jones KL, Sarah K, Gupta N, et al. Turner syndrome in Diverse Populations. 2021;182(2):303–13. https://doi.org/10.1002/ajmg.a.61461.Turner
4. Apperley L, Das U, Ramakrishnan R, Dharmaraj P, Blair J, Didi M, et al. Mode of clinical presentation and delayed diagnosis of Turner syndrome: a single Centre UK study. Int J Pediatr Endocrinol. 2018;2018(1):1–6. https://doi.org/10.1186/s13633-018-0058-1
5. Centers for Disease Control and Prevention. Epidemiology of tuberculosis. 2nd ed. Atlanta: U.S. Department of Health and Human Services; 2019.
6. Hardhana B, Sibuea F, Widiantini W. Profil Kesehatan Indonesia 2019. 1st ed. Katalog Dalam Terbitan Kementerian Kesehatan RI. Jakarta: Kementrian Kesehatan Republik Indonesia; 2020.
7. Thrasher BJ, Hong LK, Whitmire JK, Su MA. Epigenetic Dysfunction in Turner Syndrome Immune Cells. Curr Allergy Asthma Rep. 2016;16(5):1–11. https://doi.org/10.1007/s11882-016-0612-y
8. Lee YL, Wu LL. Clinical features of girls with turner syndrome in a single centre in Malaysia. J ASEAN Fed Endocr Soc. 2019;34(1):22–8. https://doi.org/10.15605/jafes.034.01.05
9. Wonkam A, Veigne SW, Abass A, Um SN, Noubiap JJN, Mbanya J-C, et al. Features of Turner syndrome among a group of Cameroonian patients. Int J Gynecol Obstet. 2015;129(3):264–6. https://doi.org/10.1016/j.ijgo.2014.11.025
10. Mousavi S, Amiri B, Beigi S, Farzaneh M. The value of a simple method to decrease diagnostic errors in Turner syndrome: a case report. J Med Case Rep. 2021;15(1):1–7. https://doi.org/10.1186/s13256-021-02673-0
11. Shankar RK, Backeljauw PF. Current best practice in the management of Turner syndrome. Ther Adv Endocrinol Metab. 2018;9(1):33–40. https://doi.org/10.1177/2042018817746291
12. Moka R, Sreelakshmi K, Gopinath PM, Satyamoorthy K. Cytogenetic evaluation of patients with clinical spectrum of Turner syndrome. J Hum Reprod Sci. 2013;6(2):129–32. https://doi.org/10.4103/0974-1208.117177
13. Hamza RT, Shalaby MH, Hamed LS, Abdulla DBA, Elfekky SM, Sultan OM. Renal anomalies in patients with turner syndrome: Is scintigraphy superior to ultrasound? Am J Med Genet. 2016;170(2):355–62. https://doi.org/10.1002/ajmg.a.37425
14. Kansra AR, Donohoue PA. Hypergonadotropic Hypogonadism in the Female (Primary Hypogonadism). In: Kliegman RM, II JWSG, Blum NJ, Shah SS, Tasker RC, Wilson KM, et al., editors. Nelson Textbook of Pediatrics. 21st ed. Canada: Elsevier Inc.; 2020. p. 11741–51.
15. Gürsoy S, Erçal D. Turner Syndrome and Its Variants. J Pediatr Res. 2017;4(4):171–5. https://doi.org/10.4274/jpr.35744
16. Bucerzan S, Miclea D, Popp R, Alkhzouz C, Lazea C, Pop IV, et al. Clinical and genetic characteristics in a group of 45 patients with turner syndrome (monocentric study). Ther Clin Risk Manag. 2017;13:613–22. https://doi.org/10.2147/TCRM.S126301
17. Kartasasmita CB, Basir D. Tuberkulosis. In: Rahajoe NN, Supriyatno B, Setyanto DB, editors. Buku Ajar Respirologi Anak. 1st ed. Jakarta: Badan Penerbit Ikatan Dokter Anak Indonesia; 2018. p. 150–78.
18. Khadka P, Koirala S, Thapaliya J. Cutaneous Tuberculosis: Clinicopathologic Arrays and Diagnostic Challenges. Dermatol Res Pract. 2018;2018. https://doi.org/10.1038/s41598-019-52332-0
19. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177(3):G1–70. https://doi.org/10.1530/EJE-17-0430
20. Irzyniec T, Jeż W, Lepska K, Maciejewska-Paszek I, Frelich J. Childhood growth hormone treatment in women with Turner syndrome-benefits and adverse effects. Sci Rep. 2019;9(1):1–9. https://doi.org/10.1038/s41598-019-52332-0
21. Lee MC, Conway GS. Turner's syndrome: Challenges of late diagnosis. Lancet Diabetes Endocrinol [Internet]. 2014;2(4):333–8. http://dx.doi.org/10.1016/S2213-8587(13)70153-0