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CASE REPORT

Isolated Feet Edema in Turner Syndrome by Prenatal Ultrasonography – Case Report and Literature Review

Jing Ma*, Li Liang*, Shanshan Liu, Kailin Yan, Li Zhang

Department of Ultrasound Medicine, Tangdu Hospital, Air Force Medical University, Xi'an, People's Republic of China

*These authors contributed equally to this work

Correspondence: Li Zhang, Department of Ultrasound Medicine, Tangdu Hospital, 569# Xinsi Road, Baqiao District, Xi'an, People's Republic of China, Email lilyzhang319_20@hotmail.com

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Purpose: Turner syndrome (TS), also known as congenital ovarian hypoplasia syndrome, is a sex chromosome abnormality caused by a complete/partial absence of the second sex chromosome with complete X chromosome. The most common findings by prenatal ultrasonography of TS include thickened nuchal translucency, cystic hygroma, cardiovascular system abnormalities, urinary system diseases, and growth retardation.

Case Presentation: We present a unique case of TS with the ultrasonographic features of dorsal skin edema on both feet and a progressive slow growth of humerus length (HL) and femur length (FL) at the second trimester of spontaneous pregnancy. We performed an extensive review of prenatal ultrasound features of TS cases from MEDLINE (PUBMED) published in English between 2000 and 2024 to prove this case's uniqueness. A 29-year-old pregnant woman with her second pregnancy after a previous missed abortion presented as the prenatal ultrasound exam for fetal structural anomalies at 24^{+3} weeks gestation revealed an edema of the dorsal skin on both feet and a short long bone of both femur and humerus for gestational age. Nuchal translucency (NT) measurement at week 13^{+6} was 1.3mm, and fetal echocardiography at week 24^{+2} showed normal. There were no markedly abnormal findings in the results of non-invasive prenatal test (NIPT) cell-free fetal DNA (cff-DNA) at 14^{+6} weeks. Then, amniocentesis was performed and the results confirmed Turner syndrome with a 45,X karyotype. The final review included 11 with a total number of 884 cases identified, among which central lymphedema such as increased nuchal translucency or cystic hygroma is the typical finding with TS by ultrasonographic examination. Peripheral lymphedema resulting in fetal substantial swelling in feet was reported in 3 cases. Fetal feet edema accompanied with growth retardation are extremely rare.

Conclusion: Peripheral lymphedema such as feet edema accompanied with long bone-involved growth retardation is rare but recognized features by prenatal ultrasonography, which should be considered as an index of chromosomal abnormalities in fetus with TS.

Keywords: Turner syndrome, ultrasonography, prenatal, edema, karyotype

Introduction

Turner syndrome (TS), also known as congenital ovarian hypoplasia syndrome, is a sex chromosome abnormality due to the complete loss or partial deletion/structural abnormalities of the second sex chromosome.[1–3] During early pregnancy, 99% of chromosomally abnormal embryos spontaneously miscarry at an incidence rate of 1 in every 2500 live-born girls.[4] Only 1% of TS fetuses whose abnormal sex chromosome is mosaic pattern can survive till birth. With the technical innovations through the decades, the analysis of cell-free fetal DNA (cff-DNA) in maternal plasma and serum, which has been called the non-invasive prenatal test (NIPT), is the innovation in the field of prenatal diagnosis.[5] The amniocenteses were performed for routine clinical indications (such as sonographic abnormalities or advanced maternal age). Ultrasonography, as a noninvasive screening modality, is useful in prenatal diagnosis of TS based on the findings including thickening of nuchal translucency (NT), cystic hygroma, cardiovascular anomalies, urinary system disorders, growth retardation etc.[6] Lymphedema is a common

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finding in fetuses with TS, especially central lymphedema such as cystic hygroma, which is found to be strongly associated with cardiac defects. Peripheral lymphedema is rare, although not specifically associated with cardiac anomalies, can result in substantial swelling in the hands and feet. Here, we present a unique case of TS in the second trimester with dorsal skin edema on both feet and a less short HL and FL by ultrasound screening.

Case Presentation

Medical records of the patient were reviewed and reevaluated to write this case report. The patient gave written consent for publication of this case report and prepared a written account of her experience. A 29-year-old pregnant woman with no history of consanguineous marriage or infectious disease/genetic history denial. Neither the pregnant woman nor her husband had any chromosomal abnormalities. It was her second pregnancy after a previous missed abortion at 8 gestational weeks. The present pregnancy was natural conception. All the pregnancy-related laboratory tests reported normal except an abnormal glucose tolerance at week 23^{+6}, and the initial treatment consists of diet and exercise to achieve glycemic goals. Nuchal translucency (NT) measured at 13^{+6} gestational week was 1.3mm. There were no markedly abnormal findings in the results of non-invasive prenatal test (NIPT) cell-free fetal DNA (cff-DNA) at 14^{+6} weeks. Fetal echocardiography at week 24^{+2} reported no evident abnormalities.

The ultrasound examination for malformation screening at 24^{+3} weeks gestation was performed by both Dr. Jing Ma and Li Liang on GE Voluson E8 with probe RAB2-5-D and about 0.7 ~0.9 cm thickness of skin and subcutaneous soft tissue on the back of fetus' feet was noted (Figure 1a and b). The value of HL was 3.5cm, FL was 3.9cm. The two values were less than two standard deviations (SD) when compared with those of gestational age (Figure 2a). No other structural anomaly was found in the heart, lungs and kidneys. Amniocentesis was recommended for advanced karyotype analysis. While waiting for the karyotype results, a routine ultrasound examination at 29^{+3} weeks gestation reported a less short HL and FL with 4.2cm and 4.9cm respectively, which was about four and three weeks' lower than what should be for the gestational age as Figure 2b indicated. The edema on the dorsal skin on the feet was severe and the thickness of the skin increased approximately to 1.0~1.08cm. Other biological measurements were in accordance with the normal reference

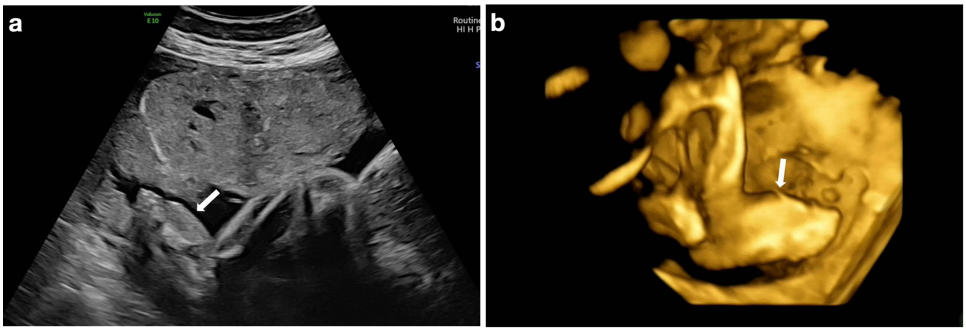

Figure 1 Prenatal ultrasonographic images of the fetus. (**a**) Two-dimensional ultrasound revealed the dorsal foot edema of the fetus. (**b**) Three-dimensional ultrasonographic image.

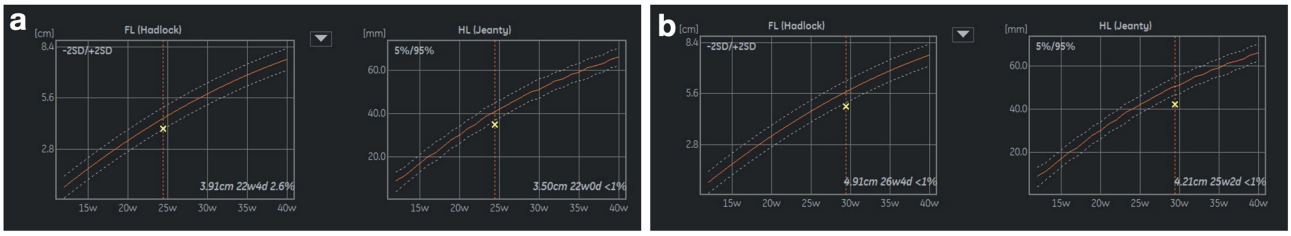

Figure 2 Growth curve analysis of FL/HL (**a**) FL/HL measured at 24^{+3} gestational weeks indicating the values were below the 5th percentile. (**b**) FL/HL measured at 29^{+3} gestational weeks indicating the value was below the 1st percentile.

value. Chromosomal karyotype analysis of the fetal tissue showed monosomy X (45, X) (Figure 3a). Then the couple decided to terminate the pregnancy. Autopsy data showed an obvious swelling on both feet (Figure 3b).

We also performed a literature review to find similar cases because the peripheral lymphedema of fetus in lower extremities is extremely rare. It was based on the survey of data available in PubMed with the following terms: "Turner syndrome and prenatal diagnosis" or "Turner syndrome and ultrasound". The case reports, case series, and cohort studies with at least one case report published between 2000.01.01 and 2024.01.31 were reviewed. Review and opinion studies were excluded as well as non-English manuscripts.

For the literature review, a total of 11 records about TS with specified prenatal ultrasonographic features were included in the final analysis (Figure 4). There were 6 single or double case reports, and 5 were single/multicenter-center case series, with the largest including 680 confirmed TS.[3] Table 1 presents all papers and extracted data.[6–16]The database includes gestational age at diagnosis, maternal age, ultrasonographic features, chromosomal karyotype and pregnancy outcome. A total number of 884 cases were reviewed, but not all data were available for all cases. The gestational age of abnormal detections by US was before 25 weeks in most cases. Out of all cases, only 1.5% (13/884) were diagnosed during the third trimester. The latest gestational age at the time of diagnosis was 40 weeks of pregnancy. The range of maternal age based on the data available was from 16 to 45, most of the pregnant women were under 35. Among these 884 cases, the most frequent karyotype in TS was 45,X karyotype (780/884, 88.2%), mosaicism was found in 11.8% of

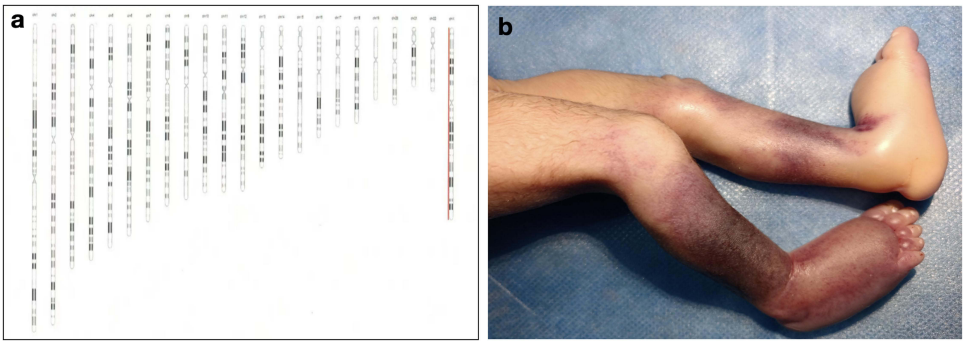

Figure 3 Chromosomal karyotype analysis and autopsy data of the fetus (**a**) Chromosomal karyotype analysis showed chromosome X monosomy (45X). (**b**) Autopsy data confirmed the edema of the dorsal aspect of both feet.

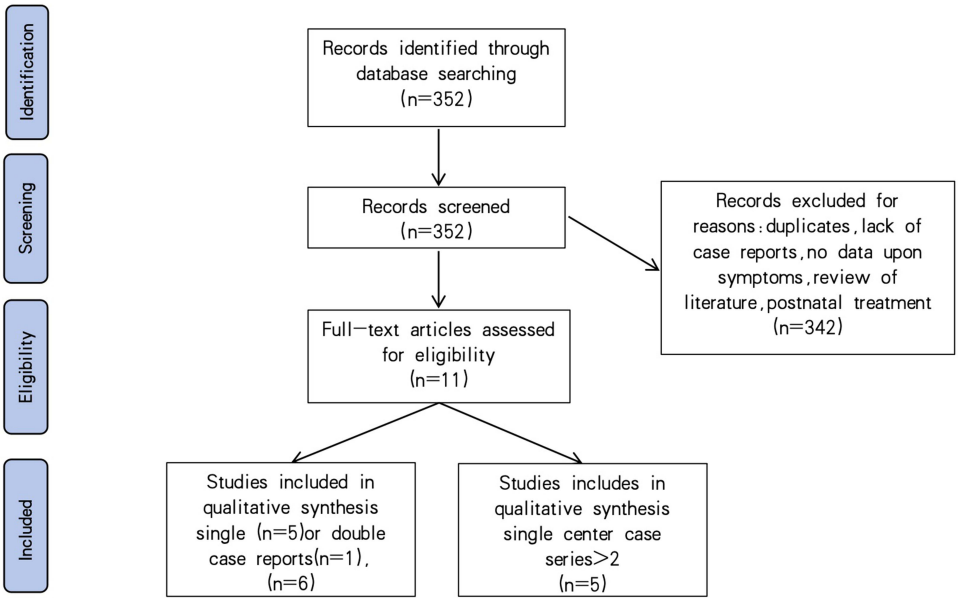

Figure 4 PRISMA flow chart of Medline Search.

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Table 1 Summary of Ultrasonographic Findings of TS

	Published Time	Case Numbers	Diagnosis Time	Maternal Age	Ultrasonographic Findings	Chromosomal Karyotype	Pregnant Outcome
Surerus E[7]	2003	53	<14	Not mentioned	Increased NT (n=47); Coarctation of the aorta (n=24); Hypoplastic left heart syndrome (n=7); Atrioventricular septal defect (n=1); Isolated tricuspid regurgitation (n=1)	45X	TOP (n=45); IUFD (n=6); LB (n=2)
Bronshtein M[6]	2003	13	14~16	29(24~35)	Cystic hygroma/ hydrops/subcutaneous edema (n=13); Short femur (n=12); Narrowed aortic arch (n=8); Ventricular septal defect (n=1); Hypoplastic kidney (n=1); Horseshoe kidney (n=2); Single umbilical artery (n=1); Omphalocele (n=1); Large fourth ventricle (n=2); Oligohydramnios (n=1); Umbilical hernia (n=1)	45X	TOP
Baena N[8]	2004	84	19 (11–40); <24 (90.5%)	29(18~40)	Cystic hygroma (n=69); Central nervous system (n=2); Congenital heart defect (n=9); Pulmonary defect (n=4); Renal defect (n=3); Abdominal wall defect (n=1); Hydrops fetalis (n=22); Nuchal thickening (n=4); Short femur (n= 2)	45X (n=76); Mosaic (n=8)	TOP (n=66); IUFD (n=11); LB (n=7)
Papp C[9]	2006	47	10~13 (n=14); 13~22 (n=33)	28.1(17~45)	Hygroma colli (n=18); Fetal hydrops (n=8); Cardiac defects (n=9); Increased NT (n=9); Ventriculomengaly (n=4); Renal abnormalities (n=8); Short femur (n=7); Choroid plexus cyst (n=6); Echogenic bowel (n=2); Echogenic intracardial focus (n=1)	45X (n=22); Mosaic (n=25)	Not mentioned
Guler I[10]	2007	1	12	27	Huge cystic hygroma and a full abdominal thickness defect with multiple loops of bowel outside the abdomen	45X	TOP
Kavanagh MC[11]	2007	1	33	19	A severely hypoplastic heart, a duplicated left kidney, and a large cystic orbital mass	45X	Born at 38 weeks and died
Chen CP[12]	2007	1	19	38	Ruptured omphalocele with extracorporeal intestines and mimicking gastroschisis	45X	TOP
Hoskovec JM[13]	2013	2	21/22	34/41	Dorsal foot edema	45X;45X	TOP/ LB at 38 weeks
Chung K[14]	2017	1	14 and 16	31	Large cystic hygroma and pleural effusion at 14^{+3} weeks gestation; Echogenic bowel and growth parameters below the 5th percentile at 16^{+1} weeks gestation.	45X	IUFD at 20 weeks
Chen HY[15]	2019	1	22	25	A septated nuchal lymphatic hygroma and hydrops fetalis, edema of the whole body, substantial pleural effusion and abdominal fluid; Bilateral syndactyly of the hands and feet.	45X	IUFD at weeks
Bedei I[16]	2023	680	13.7	28.8(19~36); 30.4(16~45)	Omphalocele (n=35); Fetal hydrops /generalized skin edema (n=403); Cystic hygroma/increased NT (n=484); Cardiac anomalies (n=228); Renal anomalies (n=31); dorsal edema of the hands and feet (n=1), single umbilical artery (n=5); umbilical cord cyst (n=2), IUGR (n=3), and hypoplastic nasal bone (n=1).	45X(n=609); Mosaic (n=71)	Miscarriage/IUFD (n=104); TOP (n=354); LB (n=50)

Abbreviations: TOP, termination of pregnancy; IUFD, intrauterine fetal demise; LB, live birth.

cases detected by prenatal ultrasound. Central lymphoedema including the increased NT and cervical hygroma were the highest incidence of ultrasonographic features of TS ranging from 71.2% to 100% in those 5 single/multicenter-center case series. Followed by cardiac anomalies, the incidence was from 10.7% to 69.2% in each study. Only 3 cases with peripheral lymphoedema of fetal feet were reported. The presence of short femur suggestive of growth retardation was found in 19 cases. Except one study involved 47 cases did not report the fetal outcome, 54.4% of cases terminated the pregnancy after diagnosed by prenatal ultrasound. Spontaneous intrauterine death occurred in 14.7% (123/837) cases and 7.3% (61/837) cases chose to continue the pregnancy. In one case, that was born at 38 weeks and died.

Discussion

Ultrasonography has played an important role that suggests an increased likelihood of TS by image rendering, which was considered as the another common NIPT technologies. For example, increased NT in the first trimester is a strong marker indicating autosomal trisomy syndromes and also common in fetuses with TS. Amniocentesis and chorionic villus sampling are two generally used prenatal diagnostic procedures, which have been considered as gold standards for prenatal genetic diagnosis. While these two methods are not routinely used as screening tests because their invasiveness may lead to a risk of miscarriage. To obtain complete fetal genetic information and avoid endangering the fetus, NIPT techniques such as cff-DNA through serological screening of mothers in the first and second trimester are usually used to find possible risks of chromosomal abnormalities, but this method is less sensitive and accurate because it needs a high efficiency separation technology to obtain the scarce fetal cells from maternal circulation. As we presented case, the test of cff-DNA reported no abnormal findings while subsequent abnormal ultrasonographic findings were presented. Given that the blood sample contains maternal DNA, the mother must also be considered as a source of the false positive result. Missed and delayed diagnoses of TS remain a major problem if no further abnormal structure was detected prenatally.

Karyotypes might affect the disease phenotype especially the structural abnormalities in the fetus, which can be detected by prenatal ultrasound scanning. Karyotypes include 45,X and mosaics (for example, 45,X/46,XX; 45,X/47, XXX). Congenital anomalies were detected more frequently by sonography in 45,X cases than in mosaics. As reported by Baena N,[8] the most frequent karyotype was 45,X (81.6%), followed by mosaicism (16.8%). Papp C[9] reported similar findings that 45,X karyotype was found in 90.4% of cases detected by ultrasound; while mosaicism was found in 9.5% of cases detected by ultrasound. Our data of literature review revealed that 88.2% cases were 45,X karyotype and 11.8% cases were mosaicism karyotype in 884 cases of TS with abnormal ultrasonographic finding. Our reported case also confirmed a 45,X karyotype.

Lymphoedema including the increased NT, fetal cervical lymphatic hygroma and systemic edema are important features of TS.[17] The presence of cystic hygroma makes the diagnosis of TS more likely. Approximately a third of TS fetuses present with persistent lymphoedema at birth,[18] leading to lymphedema sequence after birth. Central lymphedema in a TS fetus with hydrops is found to be strongly associated with cardiac defects, while peripheral lymphedema was not specifically associated with cardiac anomalies. Fetal manifestation of edema in the hands, feet, and back is extremely rare. Only 3 cases with edema of feet in the fetal period were reported. Two of them were presented as case report[13] reporting single ultrasonographic finding of dorsal foot edema in a female fetus; and the other one was presented in a retrospective study as associated findings with omphalocele.[16] Both short femur and humerus were also observed in the present case, which were characterized with a progressive slow growth with gestation weeks. Among 25 cases as five literatures reported,[6,8,9,14,16] 21 cases reported the short femur. To the best of our knowledge, this is the first report of prenatal diagnosis of TS based on the ultrasonographic finding of dorsal foot edema and progressively slow growth of FL and HL in a female fetus. The occurrence of dorsal foot edema is very crucial, which prompts the expectant mother to make up her minds to undergo the chromosomal karyotype analysis via amniocentesis.

The gestational age of diagnosing fetal feet edema by ultrasound was commonly during the second trimester. It was 21 weeks and 22 weeks documented in 2 case reports and one should be before 25 weeks. Ultrasonographic images of fetal foot could be easily obtained during the second trimester, especially after 18 weeks. The gestational age of our case was 24 weeks when routine mid-trimester fetal ultrasound scan was performed. Usually, the ultrasound scanning of fetal feet was consisted with two parts, one is to scan the plantar plane, the shape of the foot, the toes and their number are tracked and observed; the other is the longitudinal scan along the lower leg to track the positional relationship between the foot and the

lower leg, and also observe the shape of the dorsal skin and the arch of the foot. The longitudinal scanning can screen out structural deformities such as strephenopodia and rocker bottom foot. There was no abnormal findings before 24 weeks. Edema of the fetal foot may have existed, but the ultrasound resolution is incapable of detecting the detailed structural abnormalities at a small gestational age, or maybe the edema of the foot could not develop as structural abnormalities detected by ultrasound until the second trimester. It should be noted that another case report about the edema of the dorsal aspect of both feet by fetal ultrasonography at 15 weeks of gestation is a primary congenital lymphedema type I, also known as Milroy disease.[19] Because of the rarity of isolated edema, and when it is seen, the threshold for chromosomal abnormality should be lowered by the physician prompting for thorough and further evaluation.

Prenatal screening of sex chromosomes has a large risk of missed diagnosis, and non-invasive prenatal screening has certain limitations. Ultrasound and maternal serum screening are not diagnostic, and to make a prenatal diagnosis of TS, karyotype confirmation is obligatory. While typical ultrasonographic findings such as feet edema combined or not combined with other abnormalities might be a potentially useful prenatal marker of TS. Milroy disease (hereditary lymphedema type I) also should be included in the differential diagnosis because it is characterized by lower-limb lymphedema when isolated feet edema was presented. Paying special attention to the fetal feet edema on pre-natal ultrasound in general, and in history of previous abortion, chromosomal abnormality, and in presence of bone shortening.

Abbreviations

TS, Turner syndrome; NT, Nuchal translucency; cff-DNA, cell-free fetal DNA; NIPT, non-invasive prenatal test; HL, humerus length; FL, femur length; US, ultrasound; IUGR, intrauterine growth retardation; TOP, termination of pregnancy; IUFD, intrauterine fetal demise; LB, live birth.

Data Sharing Statement

This case report contains clinical data from the medical records in Tangdu hospital. Additional information is available from the first author upon reasonable request.

Ethics Approval and Informed Consent

Writing and publishing this case report was approved by Tangdu Hospital.

Consent for Publication

Written consent from the patient for case publication of potentially identifying images and clinical details.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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