

Dichorionic twin pregnancy with sirenomelia and chromosomal anomaly in 1 fetus

A case report

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Abstract

Rationale: Sirenomelia is a rare congenital malformation that threatens fetal survivals. The cases in which twin with sirenomelia and chromosomal abnormality have been seldomly reported. We reported a dichorionic twin case in which one twin had sirenomelia, the other twin had a normal phenotype, and they had different chromosomal abnormalities.

Patient concerns: The abnormal twin was found at 22 weeks by ultrasound. The sirenomelia fetus was complicated with a thoracic stenosis, enlarged rectum without anal opening, the absence of bilateral kidneys, a single umbilical artery, a single lower limb, the abnormal curvature of spine, double outlet of right ventricle, which were the indicatives of the chromosome detection.

Diagnosis: The copy number variation of the sirenomelia fetus was detected as a deletion of 4.8Mb in 11p11.12-11q11. The co-twin was found with del(Y)(q11.22q11.23), which was as the same as his father's. The mother had normal chromosome. The parents had normal phenotypes. It was firstly reported a microdeletion with sirenomelia fetus.

Interventions: There was no specific treatments for the twins.

Outcomes: Intrauterine death of the sirenomelia fetus was found at 27 weeks and postnatal death after inevitable abortion happened to the co-twin.

Lessons: Prenatal ultrasound was responsible for recognizing sirenomelia, and the detailed ultrasound scanning and chromosome detection should be done for the co-twin. The etiology of sirenomelia remains unclear, and genetic detection is also necessary for its pathogenesis research.

Abbreviation: DORV = double outlet of right ventricle.

Keywords: chromosomal abnormality, sirenomelia, twin

1. Introduction

Sirenomelia is a rare congenital malformation, and its prevalence is estimated to vary between 1/600,000–1,000,000.^[1] The incidence of sirenomelia in twins is extremely low; however, the risk of sirenomelia in monozygotic twins is nearly 100 to 150 times higher than that of dizygotic twins and singletons.^[2] Sirenomelia is characterized by the fusion of the lower

extremities, and renal agenesis, absent urinary tract and genitalia, imperforate anus, oligohydramnios, and a single umbilical artery.^[3] Sirenomelia is definitely a serious threat to fetal survival due to the associated severe malformations. More than 50% of sirenomelia cases result in stillbirths, and the live neonates with sirenomelia often die within 1 to 2 days after birth.^[4]

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Consent for publication: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

The case report was a proportion of the twin study carried out by our team, which was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Grant No. XJTU1AF2015LSL-073) and it conformed to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004), and the clinical research project (No. XJTU1AF-CRS-2015-003) has been established. The written informed consent was obtained from the patient for publication of the case details.

The manuscript has not been published in whole or in part nor is it being considered for publication elsewhere.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Here, we present a case of dichorionic twin in which 1 twin had sirenomelia while the other twin had a normal phenotype, and both fetuses had different chromosomal abnormalities. To the best of our knowledge, chromosomal abnormality of the fetus with sirenomelia has not been reported in the literature.

2. Case presentation

A 29-year-old woman patient, gravida 2, para 1, who was a farmer, had a pre-pregnancy body mass index of 28.4 kg/m^2 (pre-pregnancy weight of 70 kg and height of 157 cm). The patient's first child was female and was delivered vaginally at 37 weeks, and the birth weight was 2150 g. The child was prone to suffer from tonsil hypertrophy and upper respiratory tract infections.

The current twin gestation was spontaneously fertilized without fetal reduction management in early stage. Dichorionicity was finally demonstrated at the time of delivery. The patient had no history of chronic diseases (such as thyroid disease, hepatic disease, renal disease, endocrine disease, polycystic ovarian syndrome or anemia). Until the time of delivery, no obstetrical complications occurred (such as hypertensive disorder, diabetes mellitus, intra-hepatic cholestasis or placenta previa).

The original suspicion of sirenomelia was noted by 1 tertiary hospital (hospital 1) when the patient went for ultrasound examination at 22 weeks. Four days later, she came to our hospital for further diagnosis. The ultrasound showed that the fetus with sirenomelia (Fig. 1) was smaller than the other twin by 12 days and had oligohydramnios (no obvious amniotic pocket) and absence of end diastolic velocity in the umbilical artery. The fetus also had a series of abnormalities, including a narrow thoracic cavity, absence of bilateral kidneys and bladder, flexion deformation of the spine, double outlet of right ventricle (DORV), and a single umbilical artery. The co-twin showed

no obvious structural abnormalities, and its deepest amniotic volume pocket was 6.9 cm.

Then, the patient went to another tertiary hospital (hospital 2) for amniocentesis for the co-twin. At the same time, the patient and her husband (father of the twins) also underwent peripheral blood testing for chromosome detection. The chromosomal detection was conducted by array-based Comparative Genomic Hybridization. The results of the father and the co-twin were the same and showed the chromosomal abnormality of $\text{del}(Y)(q11.223q11.23)$. The patient and her husband decided to continue the pregnancy with the hope that the co-twin with a normal phenotype would survive. At 27⁺⁴ weeks, the patient was admitted in our hospital's emergency department due to threatened abortion. The fetus with sirenomelia was already dead (almost at 26 gestational weeks according to fetal growth measurements) (Fig. 2), as revealed by the ultrasound at admission. Then, inevitable abortion finally happened. The birth weight of the co-twin was 980 g and the Apgar score was 3, 3, and 6 for 1 minute, 5 minutes, and 10 minutes, respectively. No obvious abnormalities were found in its appearance. The co-twin was taken home by parents and soon died.

After acquiring consent from the patient, an autopsy was performed for the sirenomelia twin. The results were as follows: thoracic stenosis; an enlarged rectum without anal opening; a pair of kidney-like organs was located in the posterior peritoneum; a pair of testis-like tissue was located in the peritoneal cavity; a small bladder; a single lower limb extending from the middle to the right side of the body; the entire spine bending to the left side of the body; a flexion deformation of the right upper limb; the right fingers were overlapped strangely; cardiac malformation of DORV. The pathological examination finally demonstrated a single umbilical artery, the absence of bilateral kidneys, the presence of bilateral adrenal glands, and the presence of testis and epididymis. The sex of the fetus was male.



Figure 1. The fetus with sirenomelia with a single lower limb.



Figure 2. The fetus with sirenomelia after inevitable abortion.

At the same time, a piece of skin tissue was obtained from the sirenomelia twin for chromosomal karyotyping and copy number variations detection and finally, del(11) (p11.12q11) (GRCh37: Chr11: 50260001-55117000) was detected, which was a deletion of 4.8Mb in 11p11.12-11q11 (Fig. 3).

3. Discussion

Sirenomelia is a rare congenital syndrome, that is lethal to fetal survival. The risk factors of sirenomelia include maternal diabetes mellitus, exposure to teratogenic drugs or agents^[5] (such as, retinoic acid, cyclophosphamide, or cadmium), and a maternal

age less than 20 years or more than 40 years.^[3] In the current case, the patient had no diabetes and was pregnant at an appropriate age; however, it was difficult to determine whether the woman was exposed to certain chemical agents in her daily agricultural activities. To date, there are 2 hypotheses commonly regarding the pathogenesis. The vascular steal hypothesis^[6] proposes that sirenomelia arises from a deformed blood vessel that originates from the high abdominal aorta, which performs the function of the umbilical artery and transports a large amount of blood from the umbilical cord to the placenta; and the blood perfusion to the abdominal aorta is insufficient, eventually leading to severe malformations of the spine, lower limbs, and

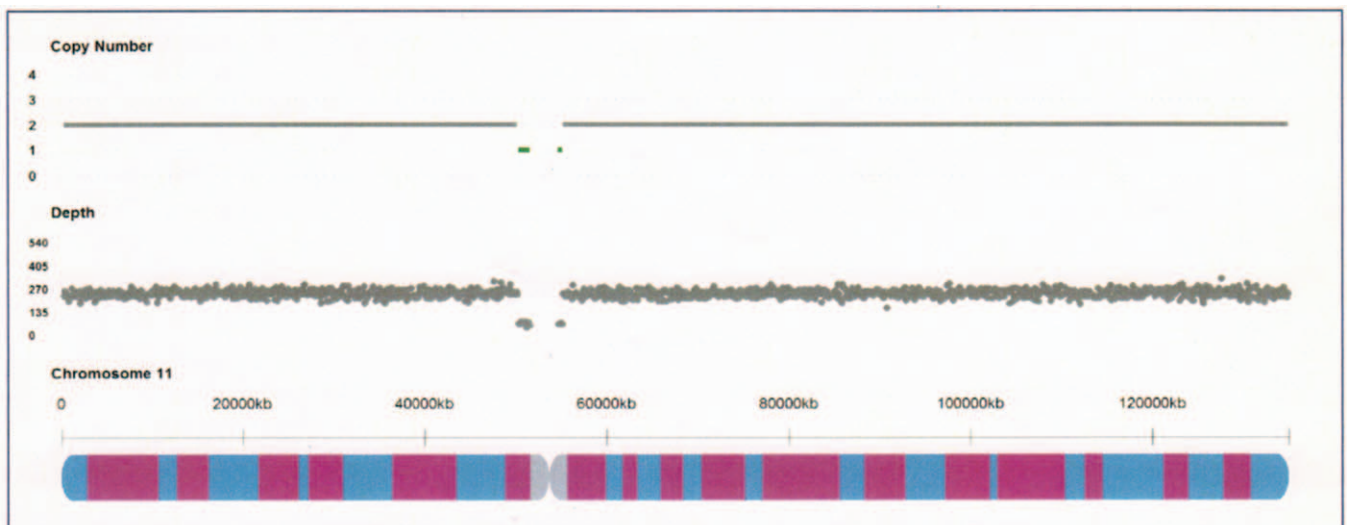


Figure 3. A deletion of 4.8Mb in 11p11.12-11q11 was found by copy number variation detection in the fetus with sirenomelia.

genitourinary system. The other hypothesis is the defective blastogenesis hypothesis,^[7] which proposes that damage to the caudal mesoderm of the embryo between 13 and 22 days in early life may result in the merging, malrotation, and dysgenesis of the lower extremities.

There are a series of characteristic sirenomelia phenotypes. A previous study has reported the frequencies for the following main malformations of sirenomelia (compiled by the results of 2 articles, the sample size was 87 cases)^[8]: vertebrae/sacrum/pelvis/lower limb (100%), anorectal (97%), renal (93%), genital (85%), lower urinary tract (57%), single umbilical artery (79%), cardiac (26%), radial limb (21%), esophageal atresia or/and tracheoesophageal fistula (5%), respiratory tract (24%), and central nervous system (8%). Oligohydramnios is a common feature in the cases with sirenomelia due to the abnormal development of the renal system. However, Pinette MG et al^[9] reported a case where the fetus was initially found with oligohydramnios at 18 weeks, but the amniotic fluid index was 11 cm at 25 weeks.

In 21 previous studies,^[10–30] twins with sirenomelia were delivered between 27 and 38 weeks, except for 1 case that was terminated in the second trimester. The co-twins with normal anatomy almost had good outcomes (a co-twin with an imperforate anus was healthy after operation^[18]). In the present case, intrauterine death of the twin with sirenomelia initially occurred, followed by spontaneous abortion. The co-twin eventually died despite normal anatomy. Based on the previous cases, it was speculated that the outcome of the co-twin without structural abnormalities might be good. With intensive prenatal monitoring, expectant management could be carried out for cases where the co-twin has normal anatomy and normal chromosome. If the sirenomelia happened in monozygotic case, prenatal monitoring of the co-twin should be enhanced when intrauterine death occurs to the sirenomelia twin. This is because the live fetus can be affected due to only 1 placenta shared by the twins and the acute transfusion by placental inter-twin anastomoses.^[31] Preterm birth is the most common adverse outcome affecting 58.5% of monozygotic twins. In total, 20% of the surviving co-twins were demonstrated to have abnormal brain alterations and the risk of perinatal death also increased in monozygotic twins.^[32] If the co-twin was found with severe structure abnormalities or detected with chromosomal abnormalities, we usually suggest not to continue the pregnancy. So a complete evaluation for the co-twin is important, which determines whether it is prudent to continue the pregnancy.

Among the previously reported cases, only 2 cases reported sirenomelia fetus with chromosomal abnormalities, including mosaicism of 69,XXX/46,XX and a de novo balanced translocation of 46,XX,t(X;16)(p11.23;p12.3).^[5,33] The other cases reported normal chromosome or without chromosome detection. To the best of our knowledge, the current case is the first to report a microdeletion of 4.8 Mb in 11p11.2-11q11 with sirenomelia fetus. It is not yet clear if sirenomelia in twins has a genetic basis.

The genes OR4A5, TRIM48, and OR4A16 are located in the involved chromosome segment. The search for the segment and genes was performed in the databases of DECIPHER, DGV, ISCA, and OMIM databases (DECIPHER is a web-based resource and database of genomic variation data from analysis of patient DNA. DGV provided a publicly accessible, comprehensive curated catalog of structural variation found in the genomes of control individuals from worldwide populations. ISCA database contains whole genome array data from a subset of the ISCA Consortium clinical diagnostic laboratories. OMIM is a comprehensive, authoritative compendium of human genes

and genetic phenotypes that is freely available and updated daily), and no related literature was found. Further studies to elucidate its underlying genetic mechanism are needed.

4. Conclusions

In summary, the prenatal ultrasound can help in recognizing sirenomelia, which is crucial due to the serious threat of sirenomelia to fetal survival, and a detailed ultrasound scanning and chromosome detection for the co-twin should be done, which may provide evidences for the possibility of survival of the normal twin. The etiology of sirenomelia remains unclear, and genetic detection is also necessary for to understand its pathogenesis.

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References

- [1] Källén B, Castilla EE, Lancaster PA, et al. The cyclops and the mermaid: an epidemiological study of two types of rare malformation. *J Med Genet* 1992;29:30–5.
- [2] Thottungal AD, Charles AK, Dickinson JE, et al. Caudal dysgenesis and sirenomelia-single centre experience suggests common pathogenic basis. *Am J Med Genet A* 2010;152A:2578–87.
- [3] Orioli IM, Amar E, Arteaga-Vazquez J, et al. Sirenomelia: an epidemiologic study in a large dataset from the International Clearing-house of Birth Defects Surveillance and Research, and literature review. *Am J Med Genet C Semin Med Genet* 2011;157C:358–73.
- [4] Ugwu RO, Eneh AU, Wonodi W. Sirenomelia in a Nigerian triplet: a case report. *J Med Case Rep* 2011;5:426.
- [5] Tonni G, Grisolia G. Sirenomelia: a review on embryogenic environmental theories, novel three-dimensional ultrasound imaging and first trimester diagnosis in a case of mosaic 69,XXX/46,XX fetus. *Arch Gynecol Obstet* 2013;288:3–11.
- [6] Stevenson RE, Jones KL, Phelan MC, et al. Vascular steal: the pathogenetic mechanism producing sirenomelia and associated defects of the viscera and soft tissues. *Pediatrics* 1986;78:451–7.
- [7] Singh C, Lodha P, Arora D, et al. Diagnosis of sirenomelia in the first trimester. *J Clin Ultrasound* 2014;42:355–9.
- [8] Jaiyesimi F, Gomathinayagam T, Dixit A, et al. Sirenomelia without vitelline artery steal. *Ann Saudi Med* 1998;18:542–4.
- [9] Pinette MG, Hand M, Hunt RC, et al. Surviving sirenomelia. *J Ultrasound Med* 2005;24:1555–9.
- [10] Roberge JL. Sympodia in identical twins. Report of a case. *JAMA* 1963;186:728–9.
- [11] Wright JC Jr, Christopher CR. Sirenomelia, Potter's syndrome and their relationship to monozygotic twinning: a case report and discussion. *J Reprod Med* 1982;27:291–4.
- [12] Biswas BP, Dawn TK, Biswas S. Combined sirenomelus and upper limb amelia in a uniovular twin. *J Indian Med Assoc* 1985;83:245–6.
- [13] Oguz A, Gokalp A, Gultekin A, et al. A case of sirenomelia, in one of a pair of identical twins, and in association with exomphalos. *Turkish J Pediatr* 1986;28:205–10.
- [14] Schwaibold H, Oehler U, Helpap B, et al. Sirenomelia and anencephaly in one of dizygotic twins. *Teratology* 1986;34:243–7.

- [15] DiLorenzo M, Brandt ML, Veilleux A. Sirenomelia in an identical twin: a case report. *J Pediatr Surg* 1991;26:1334–6.
- [16] Kapur RP, Mahony BS, Nyberg DA, et al. Sirenomelia associated with a “vanishing twin”. *Teratology* 1991;43:103–8.
- [17] Rodriguez JL, Palacios J, Razquin S. Sirenomelia and anencephaly. *Am J Med Genet* 1991;39:25–7.
- [18] Akbiyik F, Balci S, Akkoyun I, et al. Type 1 sirenomelia in one of male twins, with imperforate anus in the other male twin. *Clin Dysmorphol* 2000;9:227–9.
- [19] Managoli S, Chaturvedi P, Vilhekar KY, et al. Sirenomelia dipus in a dizygotic twin. *Indian J Pediatr* 2002;69:1093–5.
- [20] Shonubi AM, Salami BA, Falade AG, et al. Sirenomelia in one of Nigerian monozygotic twins. *Afr J Med Med Sci* 2002;31:377–9.
- [21] Assimakopoulos E, Athanasiadis A, Zafarakas M, et al. Caudal regression syndrome and sirenomelia in only one twin in two diabetic pregnancies. *Clin Exp Obstet Gynecol* 2004;31:151–3.
- [22] Horikoshi T, Kikuchi A, Tatematsu M, et al. Two cases of a fetus with sirenomelia sequence. *Congenit Anom (Kyoto)* 2005;45:93–5.
- [23] Akl MN, Saleh AA. Sirenomelia in a monoamniotic twin: a case report. *J Reprod Med* 2006;51:138–40.
- [24] Nisenblat V, Leibovitz Z, Paz B, et al. Dizygotic twin pregnancy discordant for sirenomelia. *J Ultrasound Med* 2007;26:97–103.
- [25] Guven MA, Uzel M, Ceylaner S, et al. A prenatally diagnosed case of sirenomelia with polydactyly and vestigial tail. *Genet Couns* 2008;19: 419–24.
- [26] Chen CP, Hsu CY, Lee MS, et al. Magnetic resonance imaging demonstration of sirenomelia in one fetus of a dizygotic twin pregnancy conceived by intracytoplasmic sperm injection, in vitro fertilization and embryo transfer. *Taiwan J Obstet Gynecol* 2011;50:561–3.
- [27] Nokeaingtong K, Kaewchai S, Visrutaratna P, et al. Sirenomelia type VI (sympus apus) in one of dizygotic twins at Chiang Mai University Hospital. *BMJ Case Rep* 2015;2015:bcr2014208501.
- [28] Turgut H, Ozdemir R, Gokce IK, et al. Sirenomelia associated with hypoplastic left heart in a newborn. *Balkan J Med Genet* 2017;20: 91–4.
- [29] Al Yaqoubi HN, Al Badi MM, Ambu Saidi FM, et al. A case of sirenomelia associated with hypoplastic left heart with a healthy co-twin: a rare entity. *Case Rep Pediatr* 2018;2018:9361745.
- [30] Xu T, Wang X, Luo H, et al. Sirenomelia in twin pregnancy: a case report and literature review. *Medicine (Baltimore)* 2018;97:e13672.
- [31] Fusi L, McParland P, Fisk N, et al. Acute twin to twin transfusion: a possible mechanism for brain damaged survivors after intrauterine death of a monozygotic twin. *Obstet Gynecol* 1991;78:517–20.
- [32] Mackie FL, Rigby A, Morris RK, et al. Prognosis of the co-twin following spontaneous single intrauterine fetal death in twin pregnancies: a systematic review and meta-analysis. *BJOG* 2019;126: 569–78.
- [33] Kurosawa K, Tanoshima-Takei M, Yamamoto T, et al. Sirenomelia with a de novo balanced translocation 46,X,t(X;16)(p11.23;p12.3). *Congenit Anom (Kyoto)* 2012;52:106–10.