



# Klippel–Trenaunay–Weber Syndrome—Case Report: Diagnostic Role of Fetal Autopsy and Histopathology

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## Abstract

**Objectives** The aim of this study was to evaluate a case of Klippel–Trenaunay–Weber Syndrome (KTWS) diagnosed at 15 weeks of gestation.

**Materials and Methods** A 30-year-old G<sub>4</sub>P<sub>1</sub>L<sub>1</sub>A<sub>2</sub> at 15 weeks gestation was detected with abnormal fetal right lower limb thickness and hypervascularity in both thighs. Multiseptated hypoechoic areas were detected involving skin and subcutaneous tissue of the left shoulder region, axilla, chest wall, and lower back region posteriorly extending into both lower limbs associated with cortical thickening of long bones of the lower limb. Significant subcutaneous thickening was present in the right foot along with a slow flow vascular malformation. The couple did not opt for any prenatal testing and continued the pregnancy.

**Results** The patient received routine antenatal care and at 27 weeks of gestation there was polyhydramnios with fetal demise. She delivered a macerated stillborn baby girl weighing 2.5 kg (>99th centile). Consent was obtained for external autopsy, fetal photographs, and tissue biopsy. The fetus was grossly macerated. The skin was hypertrophied and subcutaneous tissue along with bluish discoloration was present over the affected areas. Histopathology of fetal thigh tissue was suggestive of arteriovenous malformation compatible with a diagnosis of KTWS.

**Conclusions** KTWS has unique sonographic features. Confirmation can be done by clinical exome sequencing of amniotic fluid or fetal tissue.

## Keywords

- ▶ Klippel–Trenaunay–Weber syndrome
- ▶ Klippel–Trenaunay syndrome
- ▶ angioosteodystrophy

## Introduction

Klippel–Trenaunay–Weber Syndrome (KTWS) was described by Klippel and Trenaunay in 1900 and by Weber in 1907. It is a complex congenital cutaneous vascular malformation syndrome characterized by a triad of capillary and venous malformation and limb hypertrophy with or without lymphatic malformation. It usually affects only one extremity but may affect other areas as well.<sup>1</sup>

The estimated prevalence is 1 in 100,000 births.<sup>2</sup> There is no predilection for gender or any particular ethnicity, and it appears more frequently at birth, childhood, or adolescence.<sup>3</sup> Recurrence risk is extremely low as most cases are sporadic, although an autosomal dominant pattern has also been reported.

Severity of Klippel–Trenaunay syndrome is related to the timing of development in utero, component of vasculature, bone, muscle, and skin that are predominantly affected and

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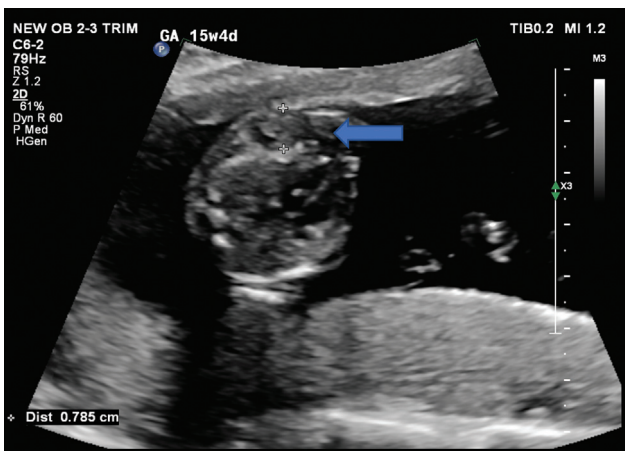
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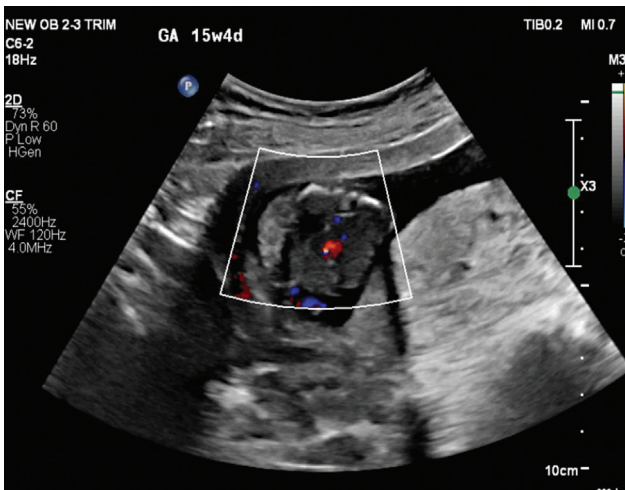
the nature of specific gene variants causing the developmental anomalies. The malformations progress over time with ongoing overgrowth and worsening venous insufficiency. The features of KTWS occur due to somatic mutations resulting in activation of phosphatidylinositol-4-5-bisphosphate 3 kinase, catalytic subunit (PIK3CA) gene and resultant cell overgrowth by dysregulation of the mammalian target of rapamycin complex 2 (mTORC2) pathway. It is part of a PIK3CA-related overgrowth spectrum. KTWS has a wide spectrum of clinical manifestations, and prognosis is related to the severity of vascular malformations.<sup>4,5</sup> Prenatal genetic diagnosis is possible and prognosis grossly depends on the size and location of hemangiomas. Cases of superficial hemangiomas have been reported to have favorable prognosis and available treatment options are resections, plastic surgery, or laser treatment.

### Materials and Methods

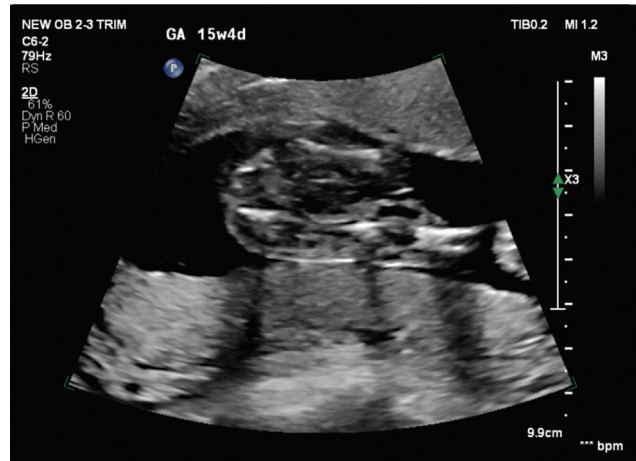
A 30-year-old G<sub>4</sub>P<sub>1</sub>L<sub>1</sub>A<sub>2</sub> presented at 15 weeks gestation with an ultrasound report suggestive of abnormal right lower limb



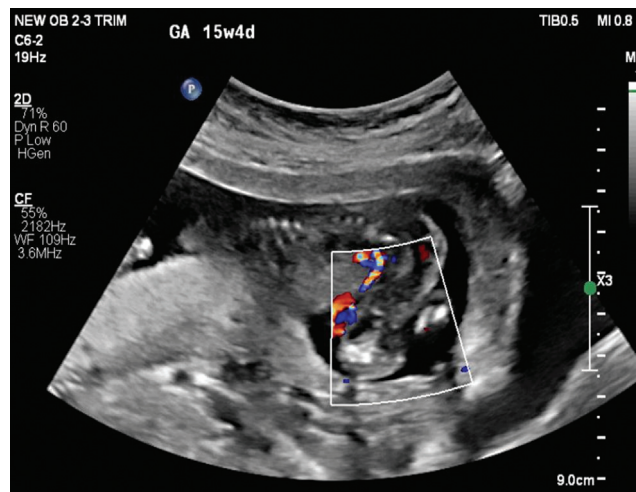
**Fig. 1** Axial section of fetal chest showing four-chamber view; there is thickening of left chest wall (blue arrow) measuring 7.85 mm.



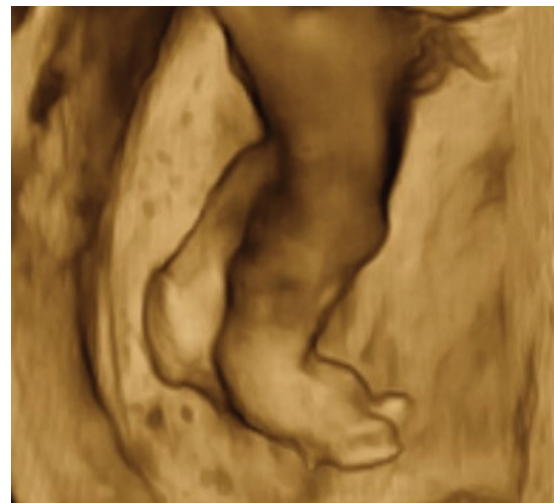
**Fig. 2** Abnormal vascular flow in involved area of chest wall.



**Fig. 3** Discrepancy between the thickness of both lower limbs.



**Fig. 4** Right lower limb with Doppler showing increased blood flow.



**Fig. 5** Three-dimensional image of the affected (right) lower limb.

thickness with hypervascularity in the thigh. The three-generation pedigree was not suggestive of any possible genetic disorder in the family. Ultrasound revealed a single live intrauterine fetus with an average gestational age of 15 weeks, 3 days with estimated fetal weight of 190 g and echogenic intracardiac foci in the left ventricle. Multiseptated hypoechoic areas were seen involving skin and subcutaneous tissue of the left shoulder region, axilla, chest wall, and lower back region posteriorly extending into both lower limbs (right > left) associated with cortical thickening of long bones of the lower limb. Significant subcutaneous thickening

involved the in the right foot along with a slow flow vascular malformation (→Figs. 1–5). A significant gap was noted between first and second toes of both lower limbs. These features were consistent with angio-osteodystrophy and a probable diagnosis of KTWS was considered. The couple was counseled regarding the diagnosis, mode of inheritance, and risk of recurrence. They were offered invasive testing for confirmation and pediatric consultation was arranged to discuss the possible outcome and prognosis. However, they did not opt for any prenatal testing and opted to continue the pregnancy. Her second trimester aneuploidy screening was



**Fig. 6** External examination of the fetus with an anterior view (A): Discrepancy between both lower limbs can be seen with hypertrophy and varicosities more prominent in the right lower limb, posterior view (B): Hypertrophy in the gluteal region, right lateral view (C): Poorly formed right foot and toes and left lateral views. (D): Hypertrophy of left trunk and shoulder and showing site of skin biopsy (E).

low risk for trisomies. Fetal echocardiography revealed normal cardiac anatomy, biometry function, and rhythm.

## Result

The patient received routine antenatal care and fetal ultrasound was done every 4 weeks. With advancing gestation, the lesion enlarged in size but remained confined to the affected sites. However, at 27 weeks there was polyhydramnios and fetal demise. She delivered a macerated stillborn baby girl weighing 2.5 kg (>99th centile). Bereavement counseling was done and consent was obtained for external autopsy, fetal photographs, and tissue biopsy. External autopsy and photography were done. The fetus was grossly macerated with peeling of skin. There was hypertrophy of skin and subcutaneous tissue along with bluish discoloration over the left shoulder and trunk region extending up to the left thigh. Similar features were noted in the entire right lower limb with gross varicosities that were more pronounced than the left lower limb (►Fig. 6A–D). The toes and the right foot were stunted with an increased gap between first and second toes in left foot. These were concordant with antenatal ultrasound features. Skin biopsy was taken from the anterolateral aspect of thigh and chest wall for histopathology (►Fig. 6E). The histopathological features were suggestive of arteriovenous malformation compatible with a diagnosis of KTWS. The immediate postpartum period was uneventful; however, she developed deep vein thrombosis in the left lower limb after 10 days of delivery. She is currently on dabigatran and using barrier contraceptives.

## Discussion

KTWS is a rare disorder that is usually sporadic with rare cases of an autosomal dominant inheritance pattern. Ivanitskaya et al reported four cases of prenatally diagnosed KTWS, with male to female ratio of 1:3. In all the cases, there was involvement of only one limb and trunk and bone asymmetry was excluded. Three of these women opted for termination of pregnancy. The fourth case continued the pregnancy and delivered a live baby boy weighing 3,750 g. On the second day of life, the neonate developed Kasabach–Merritt syndrome and 2 days later died due to severe coagulopathy and cardiac failure.<sup>6</sup>

Diagnosis of KTWS is based on limb hypertrophy associated with multiple subcutaneous cystic lesions and Doppler study of these lesions fails to exhibit internal arterial or venous blood flow suggesting that either the vascular flow rates are too low for detection or lymphangiomas constitute most of the cystic mass. It may be complicated by nonimmune hydrops fetalis, polyhydramnios, high output cardiac failure, and consumptive coagulopathy due to hemangioma-associated diffuse intravascular coagulation. Fetal magnetic resonance imaging can offer more details on the soft tissue and vasculature.<sup>7,8</sup> In the current case, there were limbs and chest involvement with polyhydramnios detected during the follow-up scan.

It has to be differentiated from lymphangioma, cystic hygroma, Beckwith–Wiedemann, Proteus, Parkes–Weber syndromes, and hereditary lymphoedema (Milroy's disease). Lymphangiomas are often single and localized, while hemangiomas in KTWS are massive, multiple, and affect a large area.<sup>9</sup>

## Conclusion

The prognosis of KTWS is usually favorable, but the quality of life is significantly affected.<sup>10</sup> Timely prenatal diagnosis of KTWS is crucial for postnatal management and choosing the right therapy for the child. KTWS should be included as a differential diagnosis when multiple surface masses of the limbs and/or trunk of the fetus or cystic lesions of the internal organs with unclear etiology are revealed on prenatal ultrasonography. Genetic testing has its own importance in diagnosing familial cases. However, KTWS can be diagnosed correctly depending on ultrasonography, fetal autopsy, and histopathology when genetic testing is not feasible.

### Funding

None.

### Conflict of Interest

None declared.

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