Recurrent lethal multiple pterygium syndrome: prenatal ultrasonographic and postmortem findings

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Introduction
Fetal akinesia deformation sequence (FADS) results from impaired fetal movement and triggered by genetic and environmental factors.\(^1,2\) Multiple pterygium syndrome is a heterogenous disease phenotypically and genetically, and it has two types on prenatal period as lethal and non-lethal (Escobar).\(^3\) Lethal multiple pterygium syndrome (LMPS) is a FADS disorder characterized by multiple pterygia (webbing) and flexion contractures of the neck, elbows and knees, and may be associated with other abnormalities such as, fetal hydrops, cystic hygroma, club foot, intrauterine growth restriction (IUGR), hypoplastic lungs and facial anomalies. It is a rare cause of recurrent midtrimester pregnancy loss.\(^4\) The inheritance may be autosomal or X-linked recessive.\(^5\) Homozygous mutations in the fetal acetylcholine receptor subunits,\(^6\) may cause fetal akinesia leading to LMPS. This brings up...
the possibility of prenatal diagnosis by genetic analysis where it is not possible at the moment. Therefore, prenatal diagnosis depends upon the patients’ history, pedigree analysis and ultrasound findings. Here, we would like to report a recurrent LMPS case with its second trimester ultrasonographic pictures and postmortem findings.

**Case Report**

A 29-year-old, gravida 5, para 4 woman was referred to our tertiary center on her 20th week of gestation. The couple was otherwise healthy and non-consanguineous. Her first pregnancy resulted in a fetal demise at 24th gestational week (GW). Autopsy revealed a hydropic male fetus with webbing of the elbows and knees and club foot deformity. She had her second pregnancy two years later. Although amniocentesis revealed a normal karyotype, the pregnancy again resulted in a fetal demise at 20th GW. Autopsy report was similar, moreover kyphoscoliosis was present. Four years later, she had delivered a healthy term female baby on her 3rd pregnancy. Two years later, her 4th pregnancy ended with a fetal demise at the 26th GW. The postmortem findings revealed a female fetus with webbed neck, elbows and knees. It is worth to note that the patient did not receive any antenatal care on her 3rd and 4th pregnancies by her will. One year later, she was pregnant again and she admitted to our maternal-fetal unit on her 20th GW although she was referred on the 11th GW. Initially, a genetic consultation was obtained in which an autosomal recessive inheritance pattern was detected according to her pedigree analysis ([Fig. 1](#)).

Ultrasonography revealed a single alive fetus where the fetal biometry was compatible with 18 weeks. A marked soft tissue edema was consistent with hydrops fetalis ([Figs. 2a and b](#)). The neck was shortened and widened. The chest appeared narrow and deformed with right pleural effusion complicated with pulmonary hypoplasia ([Figs. 2c and d](#)). A-polyhydramniotic state was recognized. There was no ascites. The posturing of the hands and feet were abnormal. No fetal movements were observed during the 30 minutes examination (even after stimulation). The upper and lower extremities were fixed, flexed and shortened. The feet were clubbed ([Figs. 3a and b](#)). All these findings were consistent with a recurrent LMPS. When the family was informed about the situation they requested the termination of pregnancy. The patient was discussed in our multidisciplinary clinical council and termination of pregnancy was decided. Labour was induced with misoprostol and a non-viable male fetus was delivered. Postmortem fetal head findings were; micrognatia, small mouth, flat nasal bridge, hypertelorism, epicanthal folds, scalp edema, low set ears and short neck ([Fig. 3c](#)). Upper and lower extremities showed flexion contractures with pterygia ([Figs. 3c and d](#)) and bilateral talipes equinovarus were present. Upon the request of the family, internal autopsy was not performed. Fetal karyotyping of the case was reported as 46-XY.

**Discussion**

Lethal multiple pterygium syndrome is the fatal form of multiple pterygium syndromes. LMPS is named for its typical fatality and for the presence of multiple pterygia and across a joint, which are associated with severe joint contractures (arthrogryposis). This autosomal recessive disorder is characterized by fetal movement loss leading to a cascade of events resulting of extremity contractures with multiple anomalies. This may be accompanied by lymphatic obstruction sequence leading to hydrops fetalis that is seen with subcutaneous edema, cystic hygroma, and pulmonary hypoplasia together.

![Fig. 1. Pedigree analysis of the family showing the autosomal recessive inheritance of recurrent multiple pterygium syndrome.](#)
utero or shortly after delivery. The inheritance may be X-linked recessive but most cases follow an autosomal recessive trait. Therefore establishing a diagnosis for LMPS is utmost important for the current and subsequent pregnancies. Common ultrasonographic findings are absence of fetal limb movements, limb flexures, hydrops fetalis and cystic hygroma. Moreover IUGR, lung and cardiac hypoplasia, diaphragmatic hernia, hydronephrosis, cerebral anomalies, polyhydranmios, abnormal faces with hypertelorism, low set ears, intestinal abnormalities and skeletal abnormalities may also be present. Cystic hygroma is an early and important sign of LMPS. Most of the reported cases in the literature are in the second or third trimester of the pregnancy but first trimester ultrasound diagnosis especially in the context of recurrence is also possible. The risk of syndrome for the offspring is affected by the inheritance pattern; therefore a comprehensive genetic workup is mandatory.

Michalk et al. showed that complete or severe functional disruption of fetal acetylcholine receptor causes LMPS. Recessive mutations of embryonal subunit of the acetylcholine G receptor (CHRNG) may cause both lethal and non-lethal MPS. Vogt et al. stated in their study performed on 15 LMPS cases that they did not meet any CHRNA1, CHRNB1 or CHRND mutations; however, they reported a homozygote RAPSN frameshift mutation in a case with lethal fetal akinesia. This information may provide great opportunities for understanding the pathogenesis of LMPS and diagnosing early and even developing some methods for establishing genetic diagnosis before implantation. In our case, it was not possible to show described genetic mutations due to the limitations on our genetic laboratory opportunities and since the family did not request an additional evaluation. The pedigree analysis of our case (Fig. 1) displayed an autosomal recessive inheritance and in this way, it was determined that both internal...
mother and father were passive carriers. By means of a pedigree study, it is possible for physician to provide a better genetical consultancy to a family. As MPS is a genetical disease free of inheritance pattern, there is no method for avoiding to catch the disease for now. Although sperm donation is a method that can be recommended to families, it seems impossible to practice for many families.

**Conclusion**

This finding may offer an insight for the pathogenesis of LMPS leading to an earlier and even preimplantation genetic diagnosis of LMPS. Although these developments would be a potential for some form of interventional therapy in the future, today the gold standard diagnostic approach in such a rare case is obstetric ultrasound.

**Conflicts of Interest:** No conflicts declared.

**References**