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Case Report

Mermaid Syndrome Associated with VACTERL-H Syndrome

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Abstract

Mermaid syndrome or sirenomelia is an extremely rare congenital malformation with an incidence between 1.5 and 4.2 per 1,000,000 pregnancies. Association of mermaid syndrome with VACTERL-H syndrome is extremely rare, with only two cases reported so far in the literature. We present a new case of type I sirenomelia associated with VACTERL-H syndrome and review the relevant literature.

A 15-year-old female patient was admitted to the Department of Pathological Pregnancy at St George University Hospital, Plovdiv with progredient abortion during her first pregnancy. She had low socioeconomic status, negative history of concomitant diseases and addictions. The patient avoided prophylactic intake of folic acid during her pregnancy. Prenatal ultrasound found a malformative fetus. Consequently, magnetic resonance imaging was performed which established the presence of hydrocephalus and defects in the lower part of the spine. These pathological findings indicated interruption of pregnancy at 20 weeks of gestation. The fetopathological examination found sirenomelia type I associated with myelomeningocele, hydrocephalus, anal imperforation, single umbilical artery, bilateral renal and ureteric agenesis, bladder agenesis, tracheo-esophageal fistula, agenesis of external genitals, monkey fold of the left palm of the hand, also known as VACTERL-H syndrome.

Our case demonstrates that mermaid syndrome and VACTERL-H syndrome represent different manifestations of a single pathological process that results in disorders of the blastogenesis at different stages during embryonic development.

Keywords

mermaid syndrome, pregnancy, sirenomelia, VACTERL-H syndrome

INTRODUCTION

Mermaid syndrome (MS) is an extremely rare congenital lethal malformation with an incidence between 1.5 and 4.2 per 1,000,000 pregnancies.[1] This anomaly is characterized by conjoint lower limbs or one leg, hypoplasia or agenesis of the genital organs and kidneys with absence of bladder, single umbilical artery, abnormalities of the spine and skeleton.[2] It is often associated with anomalies of the central nervous system, such as alobar holoprocephaly and lumbar myelomeningocele, and malformations of the gastrointestinal tract.[3] Less commonly, lung hypoplasia, diaphragmatic hernia, and cardiac abnormalities are observed.[4] MS can be of 7 types: I – all the bones of the thigh and leg are present; II – one fibula; III – missing fibulae; IV – partially fused femurs and fully fused fibulae; V – partially fused femurs; VI – one femur and fibula; VII – one femur and missing fibula.[5]

We present a new case of type I MS associated with VACTERL-H syndrome and review the literature.

CASE REPORT

A 15-year-old female patient was admitted to the Department of Pathological Pregnancy at St George University Hospital, Plovdiv with progredient abortion during her first pregnancy. She had low socioeconomic status, negative history of concomitant diseases and addictions. The patient avoided prophylactic intake of folic acid during her pregnancy. Prenatal ultrasound found a malformative fetus. Consequently, magnetic resonance imaging was performed which established the presence of hydrocephalus and defects in the lower part of the spine. These pathological findings indicated interruption of pregnancy in the 20th gestation week due to medical issues inconsistent with life.

The X-ray examination of the fetus confirmed evidence of severe defects in the lower spine and type I MS ***(Fig. 1A, 1B)****.The fetopathological examination established fetal growth retardation, myelomeningocele, hydrocephalus, anal imperforation, single umbilical artery, bilateral renal and ureteric agenesis, bladder agenesis, tracheo-esophageal fistula, agenesis of external genitals, female internal gonad and monkey fold of the left palm of the hand* ***(Fig. 2)****. The fetopathological diagnosis was MS with VECTERL–H syndrome. All procedures presented here were approved by the Ethics Committee of the Medical University of Plovdiv (Protocol 5, 29.09.2016) and were in accordance with the Helsinki Declaration of 1975, as revised in 2000.*

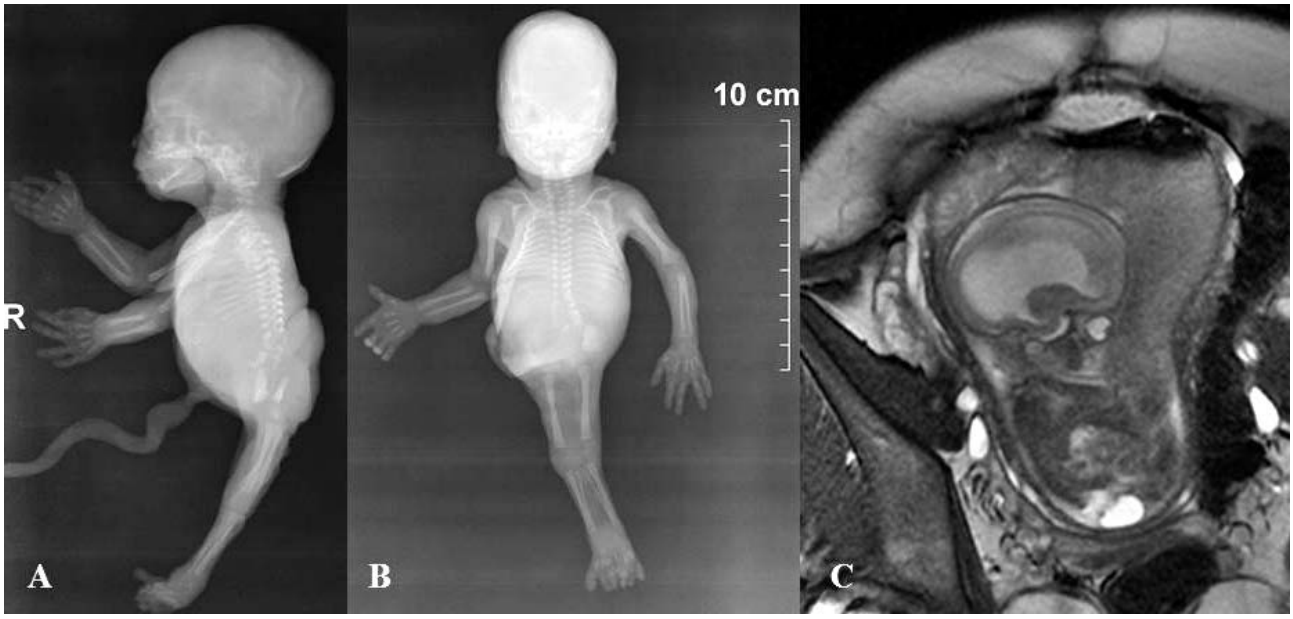

Figure 1. Sirenomelia. **A** and **B**. Radiography (face and profile). One lower limb with bones for two lower limbs and feet; **C**. Prenatal MRI visualizes the available hydrocephalus and defects of the lower spine and spinal cord.

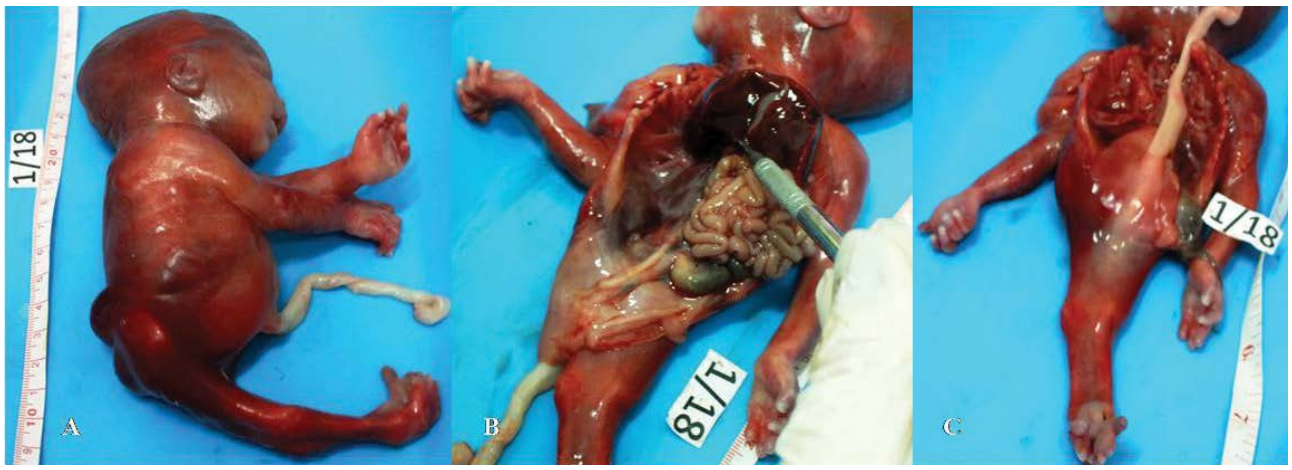

Figure 2. Sirenomelia. **A**. Profile picture of the fetus. Cystic lumbosacral spina bifida (arrow); **B**. Posterior view of fetus, Cystic lumbosacral spina bifida (arrow); **C**. Agenesis of right phrenic dome, agenesis of the internal genitalia and bladder, blindly ending colon; **D**. Agenesis of external genitalia.

DISCUSSION

Presence of single umbilical artery in cases of MS was found in 60% of cases, which was also confirmed by our case.[4]

According to Kırımi et al., the prevalence in males was threefold higher than females. On the other hand, Orioli et al. reported that the fetus gender cannot be established in 46% in the cases with sirenomelia.[6,7] Our case presented with agenesis of the external genitalia, but the fetal autopsy showed evidence of female internal genitalia. In a large epidemiological study, Orioli et al. noted a significant risk for the occurrence of MS in mothers younger than 20 years, which is confirmed in our case.[7]

Until recently, MS was considered to be the most severe form of caudal regression syndrome (CRS), but currently, it is believed that these are two separate anomalies with different embryonic origin.[8] Both conditions share common specific anomalies, but the presence of an aberrant umbilical artery or "persistent vitelline artery" is a major anatomical finding that distinguishes sirenomelia from caudal regression syndrome.[9]

Teratogenic agents during the 3rd gestation week may interfere with the formation of the notochord, leading to abnormal development of caudal structures and defect of the caudal mesoderm with occurrence of CRS between the 28th and 32nd gestational days.[9] The etiology of MS is not completely clear. Several mechanisms are considered to be involved in its occurrence: blastogenesis disturbance leading to a deficiency of the caudal mesoderm, mechanical defects due to lateral compression of amniotic folds and trophic defects due to insufficient blood supply in the posterior region.[8] According to Schiesser et al., impaired blood supply to the caudal end of the embryo due to vascular deprivation is the most likely cause of MS.[10] According to this hypothesis, abnormal vasa vitelina leads to a reduction of arterial blood flow to the caudal end of the embryo which disrupts its normal development and causes abnormal formation of the lower limbs.[9] In most of the fetuses with MS, the umbilical artery is connected to the upper mesenteric arteries, which disrupts the blood supply. According to another hypothesis, the caudal mesoderm is damaged during blastogenesis of the embryo which causes complete malformation of the caudal part of the latter.[3] MS is a typical example of a primary blastogenesis defect affecting many of the midline primordial cells during the final stages of gastrulation at the level of the caudal eminence that is responsible for the production of mesenchyme for the lower limbs and perineum, somites and vertebrae until the closure of the caudal neuropore. Disruption of the morphogenetic processes occurring in the region of the caudal eminence can lead to malformations of the sacrococcygeal vertebrae, various degrees of caudal dysgenesis, and MS.[11]

In mice experiments, Garrido-Allepuz et al. found that those with sirenomelia lack Cyp26a1, an enzyme that breaks down retinoic acid, which leads to a reduction of signalling of the morphogenetic protein in the caudal part of the embryo.[11] The phenotypes of these mutant mice suggest that sirenomelia in humans is associated with an excess of retinoic acid signalling and a deficiency of Bmp signalling in the caudal part of the embryo.[12]

Approximately 10% of fetuses with MS have concomitant neural tube defects, as the most common anomalies reported in the literature were allobar holoprosocephaly and lumbar meningomyocele, also observed in our case.[3,13]

Most of the anomalies in fetuses with MS are identical to those associated with VACTERL syndrome, which occurs between 1 in 10,000 and 1 in 40,000 children, approximately <1-9 per 100,000 children. It is an acronym for a combination of at least three of the following anomalies: vertebral defects (V), anal atresia (A), heart defects (C), tracheo-esophageal fistula (TE), renal abnormalities (R), and limb defects (L).[13] Our fetus has all of these malformations except for heart defects.

There is insufficient clinical and genetic evidence of heterogeneous etiology in patients with the VACTERL syndrome. Genetic factors associated with the VACTERL syndrome include chromosomal deletions or duplications, mitochondrial dysfunction, as well as mutations of the HOXD13, ZIC3, PTEN, FANCB, and FOXF1 genes.[14] A limited number of external and internal factors can also lead to the development of the disease, such as diabetes mellitus, long-term treatment for infertility, harmful exposure during pregnancy in geographical areas near mines and groundwater.[15]

The combination of VACTERL syndrome with hydrocephalus was first described in 1984 and since then this condition was described as "VACTERL-H syndrome".[16] In some of the cases, VACTERL-H syndrome was associated with an X chromosome inheritance of Fanconi anemia, combined with a mutation of the FANCB gene.[17] In the rest of the cases with VACTERL-H syndrome, there was no combination of Fanconi anemia and chromosome abnormalities, which is confirmed by our case.

MS associated with VACTERL is a rare condition and only twenty cases have been reported in the literature.[18] According to Vasisht et al., the case of the MS associated with VACTERL-H syndrome described by them is only the second after the first described by Onyeije et al., which makes our case the third case reported in literature.[19,20]

CONCLUSIONS

From what we currently know about this syndrome we can conclude that the MS and the VACTERL syndrome are probably different manifestations of a single pathological process that causes disorders of blastogenesis at different stages during embryonic development.

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Синдром русалки, связанный с синдромом VACTERL-H

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Резюме

Синдром русалки или сиреномелия – чрезвычайно редкий врождённый порок с частотой от 1.5 до 4.2 на 1 000 000 беременностей. Связь синдрома русалки с синдромом VACTERL-H чрезвычайно редка, и в литературе описано только два случая.

Больная 15 лет поступила в отделение патологической беременности Университетской клиники «Св. Георгий», Пловдив, с прогрессирующим абортом во время первой беременности. У неё был низкий социально-экономический статус, в анамнезе не было сопутствующих заболеваний и зависимостей. Во время беременности пациентка не принимала фолиевую кислоту с профилактической целью. Пренатальное УЗИ выявило уродливый плод. Впоследствии была проведена магнитно-резонансная томография для выявления гидроцефалии и дефектов нижнего отдела позвоночника. Эти патологические находки были индикатором прерывания беременности на 20-й неделе беременности. Фетопатологическое обследование выявило сиреномелию I типа, связанную с миеломенингоцеле, гидроцефалию и анальную имперфорацию, единственную пупочную артерию, двустороннюю агенезию почек и мочеточника, агенезию мочевого пузыря, трахео-пищеводный свищ, агенезию гениталий, обезьянью складку левой ладони, также известную как синдром VACTERL-H.

Наш случай показывает, что синдром русалки и синдром VACTERL-H являются разными проявлениями одного и того же патологического процесса, который приводит к нарушениям бластогенеза на разных его стадиях во время эмбрионального развития.

Ключевые слова

синдром русалки, беременность, сиреномелия, синдром VACTERL-H