Case Report

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Sirenomelia Apus with Cystic Dysplastic Kidney A Rare Polymalformative Syndrome

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Abstract

Sirenomelia is a lethal form of caudal regression anomaly which shows fusion of the lower limbs with a spectrum of anomalies affecting musculoskeletal, genitourinary and gastrointestinal systems.It resembles a mermaid in Roman mythology, with upper body of a human and the lower half resembling the tail of a fish.We report a case of anomalous fetus diagnosed at 18 weeks of gestation born to a non-diabetic mother.External phenotype showed fused lower limbs, no discernible external genitalia, imperforate anus,hypodactyly, ectopic cystic dysplastic kidneys and Potter's syndrome with single umbilical artery. Maternal diabetes has been associated with caudal regression syndrome and sirenomelia. Here we report a case of Sirenomelia with Potter's syndrome and cystic renal dysplasia not associated with gestational diabetes mellitus. The presence of cystic renal dysplasia in our case would further endorse the mesodermal defect in caudal regression syndrome. The possible use of genetic analysis will help to analyse the underlying molecular mechanisms of caudal regression syndrome associated with cystic renal dysplasia.

Keywords: Sirenomelia; Cystic Renal Dysplasia; Potter' Syndrome; Hypodactyly.

Introduction

Sirenomelia is an extremely rare anomaly with an incidence of 0.8-1 case/100000 births.[1,2,3] It shows fusion of lower extremities with anomalous musculoskeletal, genitourinary and gastrointestinal systems. Sirenomelia is the severe form ofCaudal regression syndrome (CRS)that encompasses a wide spectrum of congenital anomalies resulting from an embryonic defect due to injury to the caudal mesoderm in the early gestation during gastrulation.[4,5] When features of Potter's facies are combined with olighydramnios and pulmonary hypoplasia, it is known as Potter's syndrome.[6]

Sirenomelia has a strong association with maternal diabetes and 10-15% of fetuses with this anomaly have been born to diabetic mothers.[1,7] Renal Cystic Dysplasia (RCD) has been reported to be associated with caudal regression syndrome.[5]

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Case Report

A 22 year old primigravida on antenatal ultrasonography scan was detected to have anomalous fetus with lower limb deformity, absent kidneys and anhydramnios at 18 weeks of gestation. The pregnancy was terminated and the fetus weighed 340 grams.

External examination showed fused lower limbs, bilateral absent feet, no discernible external genitalia, imperforate anus, left upper limb hypodactyly and Potter's facies (large low-set ears, prominent epicanthic folds, hypertelorism, flat nose and receding chin)(Fig.1). Internal examination showed left lung hypoplasia, absent kidneys in lumbar area, ectopic cystic kidney in pelvic cavity attached to mesentry and a single umbilical artery(Fig. 2).

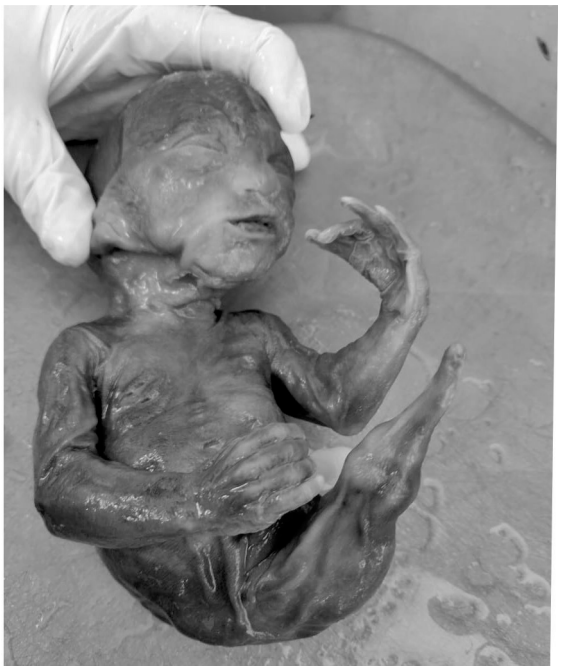

Fig. 1: External anomalies: Fused lower limbs, Left upper limb hypodactyly (4 fingers)- Absent thumb, imperforate anus, indiscernible external genitalia and Potter' facies(large low-set ears, prominent epicanthic folds, hypertelorism, flat nose and receding chin)

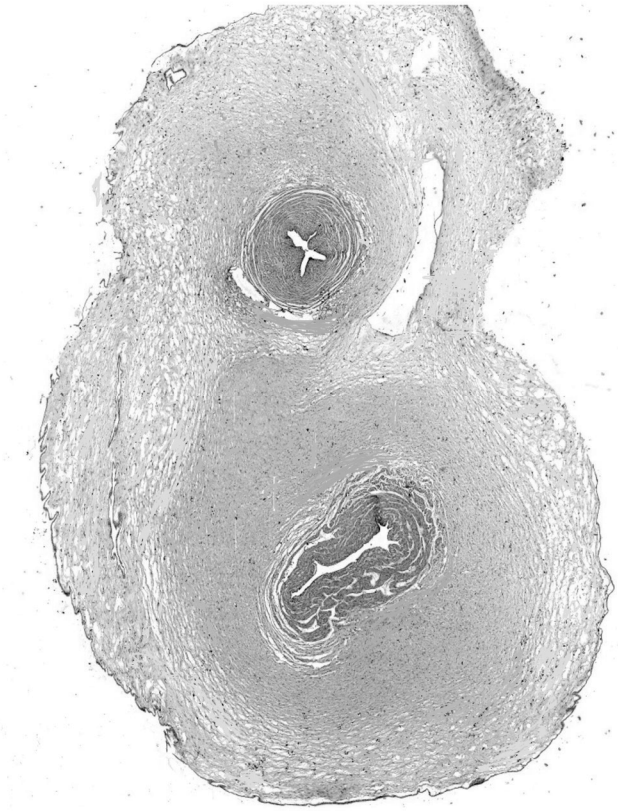

Fig. 2: Cut section of umbilical cord showing a single umbilical artery and a vein.

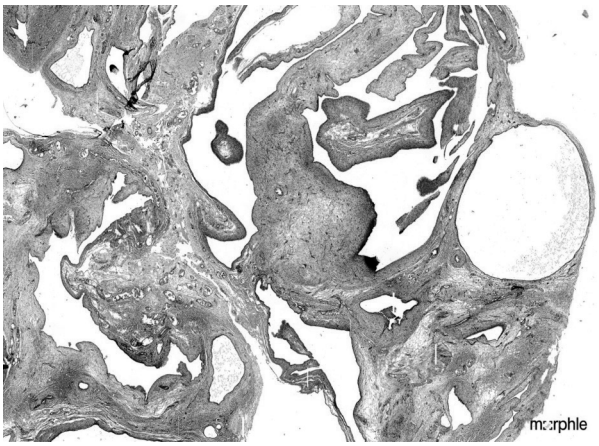

Fig. 3: Cystic dysplastic kidneys displaying multiple cystic spaces lined by flattened cuboidal epithelium.

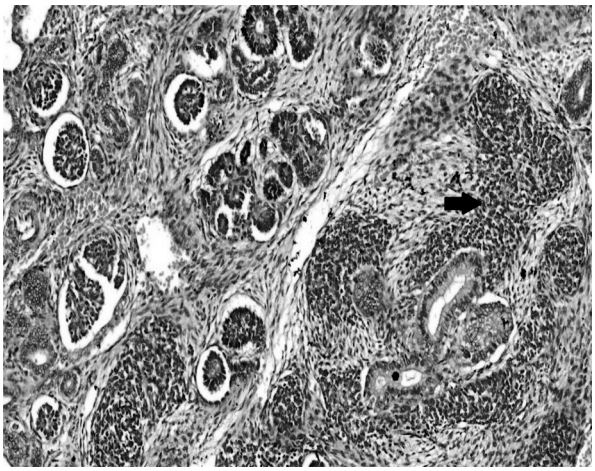

Fig. 4: Foci of nodular blastema -undifferentiated cells (arrow) and primitive glomeruli.

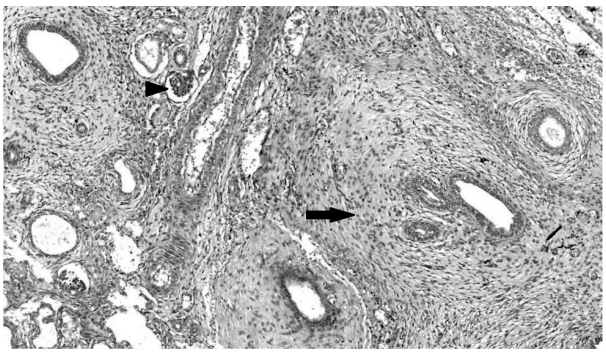

Fig. 5: Islands of undifferentiated mesenchyme, immature collecting ducts with fibromuscular collars (arrow) and primitive glomerular structures (arrowhead).

Microscopic examination of the cystic mass showed renal glomeruli embedded in a stroma consisting of multiple cystic spaces lined by flattened epithelium(Fig.3). Foci of nodular blastema composed of undifferentiated cells were seen(Fig 4). Immature collecting ducts with fibromuscular

collarsand primitive glomerular structures(Fig 5) werediagnostic of cystic renal dysplasia-Potter Type 2. A diagnosis of SirenomaliaApus with Potter's syndrome, hypodactyly and renal cystic dysplasia was made.

Discussion

Caudal regression syndrome (CRS) encompasses a wide spectrum of fetal anomalies with varied degrees of severity. The most severe extreme end of the spectrum is fusion of the lower limbs with major organ malformations, known as sirenomelia, while the mildest form is imperforate anus.[5] Sirenomelia is associated with visceral abnormalities encompassing lumbosacral and pelvic malformations, such as sacral agenesis, malformed vertebrae and hemivertebrae, absent or malformed external and internal genitalia, imperforate anus, cleft palate, pulmonary hypoplasia, and cardiac defects.[7] Sirenomelia is incompatible with life with more than half the cases resulting in stillbirth and those born alive die within a day or two of birth because of severe visceral anomalies involving abnormal kidney and bladder development.[6,7]

In 1987, the theory of vitelline artery steal was hypothesised by Stocker and Heifetz and reported that consistently all patients with sirenomelia had a large umbilical artery derived from a persistent vitelline artery. Thevitelline artery reduces the bloodflow and feeds the caudal portion of the embryo by diverting bloodflow from the embryo to the placenta. Theremaining branches of the aortic arteries are either absent or hypoplastic.[2,3] The end result is sacral hypoplasia, renal agenesis, bladder and ureteral hypoplasia, deficiency of the genitalia, and malformations of lowerlimbs. The second hypothesised theory is of defective blastogenesiswith hypoperfusion, leading to insufficient growth and incomplete development of the caudal region.[3]

Sirenomelia has been hypothesized to be caused by sporadic mutation and thought to be the result of combined genetic and environmental components.[5,7] Though genetic defects in humans are still unknown in the mermaid syndrome, two defective genes Cyp26a1 and BMP7(bone morphogenic protein) genes have been identified in mice for the birth of a mermaid neonate.[3]

The environmental risk factors described for caudal regression anomalies are multiple such as retinoic acid, maternal diabetes and heavy metals.[7] Mothers younger than 20 years and older than 40 years are known to be vulnerable.[1] Gestational diabetes mellitus has been implicated in 10–15% of affected fetuses.[1,3,7] An association with drug abuse such as cocaine, has also been described in the causation off sirenomelia in a few reported cases.[1,7] The present case showed no association with maternal diabetes or drug abuse which can be an additional plea to other environmental causes and genetic causes which need further study.

Stocker and Heifetz classified sirenomelia into seven types Type I to type VII, based on the presence of skeletal elements inlower limb. In type I, the mildest form, the fusion only affects superficial tissues with all bones in the two fused limbs being present. In type VII, the most severe form, only a single lower limb bone is present, with no indication of legs or feet.Sirenomelia used to be classified as sympusdipus or symmeliawhen two feet were present, sympusmonopus or uromelia when only one foot was discernible, and sympusapus or sirenomeliaapuswith no evidence of distal foot.8In our case, based on external examination finding of absent feet, it is classified as SirenomeliaApus.

Potter syndrome and Potter facies, a facial abnormality has been described to be frequently asssociated with cases of sirenomelia, as in our case. Potter's syndrome is a triad of Potter'sfacies (large, low-set ears, prominent epicanthal folds, flat nose, hypertelorism, and receding chin), oligohydramnios and pulmonary hypoplasia. This syndrome is almost invariably associated with bilateral renal agenesis.[1,6]

Our case had hypodactyly with absent thumb and hypoplastic thumb has been previously reported to be associated with sirenomelia.3,6Single umbilical artery has been associated in 100% cases ofsirenomelia as in our case.[9]

Renal Cystic Dysplasia (RCD) has been documented to be associated with caudal regression syndrome.[5,10] In a fetopathologic study of 74 cases of renal cystic diseases, RCD was isolated in 19% cases, associated with obstructive uropathy in 12% cases and polymalformative syndrome in 69% cases. Among the unclassified polymalformative syndromes, the renal dysplasia was part of caudal regression syndrome (CRS) in 6/18 of fetuses.[5]As the kidneys and ureters are developed from the mesoderm, it can be hypothesised that, the presence of cystic renal dysplasia in cases of sirenomelia would affirm the mesodermal defect in caudal regression syndrome as in our case.[10]

Renal cystic disease in the present fetus was type 2 according to potter classification:

type 1;Infantile polycystic kidney disease

(ARPKD Autosomal recessive polycystic kidney disease), type 2;cystic dysplastic kidney [MCDK-multicystic dysplastic kidney disease]), type 3; adult polycystic kidney disease (ADPKD); and type 4; urinary outflow obstruction (obstructive dysplasia).[11] Renal dysplasia is diagnosed by primitive ducts with a fibromuscular collar and lobar disorganization. The other microscopic findings include metaplastic cartilage, bone, nodular renal blastema, and proliferating nerves.[12]

Caudal regression syndromes with multicysticrenal dysplasia are frequently sporadic. A pilot study by Porsch et al.has recently identified three candidate genes, the known tumor suppressors, PDZD2, GLTSCR2 and PTEN by whole exome sequencing and copy number variation analyses. These have been previously identified in a patient affected with VACTERL: association of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. This study makes it imperative to screen these candidate genes in multicystic renal dysplasia associated with CRS.The current use of whole exome sequencing may help to elucidate the underlying molecular mechanisms of cystic renal dysplasia of unknown etiology associated with caudal regression syndrome.[10]

Conclusion

Antenatal ultrasonography as early as 13-15 weeks of pregnancy can detect gross fetal structural anomalies associated with caudal regression syndrome. Early diagnosis is imperative for immediate termination of pregnancy that can be safely advised to the mother to prevent maternal morbidity and mortality. Further molecular and genetic studies are warranted for the identification of possible candidate genes in a polymalformative syndrome.

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