



Cloacal dysgenesis sequence associated with esophageal atresia and tracheoesophageal fistula: A case report and review of literature

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ABSTRACT

Absence of any orifice in perineum, presence of smooth perineum, and absence external genitalia are characteristic of cloacal dysgenesis sequence (CDS). Newborn of 40w gestational age, born to mother with oligohydramnios, had very low APGAR scores, and was put on ventilator. Child had dysmorphic facies, short neck, compressed chest, no urinary bladder swelling, absence of any perineal orifice, a raised fold of skin at the site of phallus and bilateral talipes calcaneovalgus. Esophageal atresia (EA) was diagnosed clinically and radiographically. Pulmonary hypoplasia, distal tracheoesophageal fistula (TOF), thin, flat and broad cervical vertebrae with spina bifida, partial sacral agenesis and cardiac anomalies were demonstrated by radiographs and echocardiography respectively. Child progressively more desaturated on ventilator and died at 16h after birth before detailed assessment including sex could be done. CDS results from failure of urorectal septum to fuse with cloacal membrane at 7th week of intrauterine life. It can occur in male and female. CDS is lethal resultant from associated severe pulmonary hypoplasia and renal insufficiency. Very rarely such child is born alive as in our case. Association of CDS with EA+TOF is extremely rare. In view of 5 long-term survival reports of CDS, prenatal diagnosis is warranted and treatment should be initiated.

Key Words: Cloacal dysgenesis sequence, absent perineal orifice, absent external genitalia, compressed chest, urorectal septum malformation sequence.

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Introduction

Combined abnormalities of anorectal region and genitourinary region are often complex and challenging to pediatric surgeon. The exact diagnosis may be confusing and treatment of such case can be disappointing. Absence of any orifice in perineum, presence of smooth perineum, and absence external genitalia are characteristic of cloacal dysgenesis sequence (CDS) [1-3]. Most cases were stillborn, or

pregnancy terminated. Very few cases were born alive and died in immediate neonatal period [3]. This condition is incompatible with life. We report a case of CDS born alive, also associated with esophageal atresia and tracheoesophageal fistula. Such an amalgamation is reported extremely rarely.

Case report

Newborn of 40w gestational age was born of caesarean section due to breech presentation and premature rupture of membranes. Mother was 23y old gravida 4, para 3, abortion 1. This pregnancy was unmonitored, and when she presented to emergency room with abdominal pain at 40w, by ultrasound scan, oligohydramnios was detected. Newborn APGAR scores were 0 at 1', 2 at 5' and 4 at 10'. Child was put on ventilator immediately after birth but was having SPO₂ around 30% only. Bodyweight was 1950g. Child had dysmorphic facies with low-set ears and short neck (Fig.1).



Fig. 1. Dysmorphic facies with low-set ears and short neck.

The chest was very compressed and narrow, but had normal air-entry to both lungs. Abdomen was not distended and no mass was palpable. The perineum was very peculiar because it was smooth and showed no anal, vaginal or urethral opening (Fig. 2).



Fig. 2. Smooth perineum with no orifice and no external genitalia but with a raised skin fold in the place of phallus.



Fig. 3. Lower limbs showing hyperextended knees and bilateral talipes calcaneovalgus.

In the place of phallus, an elevated fold of skin was present. No labia majora, labia minora, or scrotal rugae was seen. Both hip-joints were hyperflexed, both knees were hyperextended and bilateral talipes calcaneovalgus was present (Fig. 3).

A 10F infant feeding tube introduced through mouth was stopped in the upper esophagus about 10cm from lower gum. The kinked feeding tube was seen by chest radiograph, which confirmed esophageal atresia (EA) (Fig. 4).



Fig. 4. Skiagram of neck and chest showing nasogastric tube kinked with tip upwards in the upper thorax. Cervical vertebrae are flat, thin and broad with spina bifida, and compressed chest.

Chest radiograph also confirmed compressed chest, very small volume lungs, normal cardiac shadow and cervical vertebral anomalies in the form of thin, wide vertebrae with spina bifida. Abdominal radiograph showed gas-filled bowel loops, indicative of distal tracheoesophageal fistula (TOF) (Fig. 5).



Fig. 5. Skiagram of chest and abdomen showing gas-filled bowel loops, presence of upper three sacral vertebrae and narrow bony pelvic outlet.

Only 3 sacral vertebrae were seen and pelvic outlet was very narrow as seen in radiograph. Echocardiograph revealed small atrial septal defect and small patent ductus arteriosus. Routine blood examination showed hemoglobin 15.6gm/dl, white blood cell count $14.04 \times 10^3/\mu\text{l}$, platelet count $196 \times 10^3/\mu\text{l}$, neutrophils 24.1%, lymphocytes 60%, eosinophils 10.1%. Continuous upper esophageal pouch suction and intravenous fluid administration was instituted. Child progressively more desaturated on ventilator and died at 16h after birth.

Discussion

Our patient had morphological features of CDS and compression of chest, face and limbs.

CDS is an extreme hindgut malformation occurring in 1:50,000 to 250,000 neonates [1,3,4]. It has smooth perineum, no urethral, vaginal, or anal opening, lack of labioscrotal development, and a phallus-like structure. Typically, the bladder, vagina, and colon each end blindly, but persistent cloaca without perineal orifice can be seen [3-5]. Robinson and Tross categorized systemic findings into 3 types—primary malformations of genitourinary system, malformations due to external compression, and anomalies involving other systems [3]. Patients can be males or females. Labia majora and minora are absent in females. Scrotum and penis are absent or hypoplastic in males [1,2]. Compressive features, secondary to oligohydramnios, such as Potter facies, congenital talipes equino-varus and pulmonary hypoplasia are common in CDS patients [4]. Reduced production of a pulmonary growth factor or reduced proline production by malformed kidneys which cause decreased collagen formation also result in hypoplasia of lung [2]. CDS with bilateral renal agenesis without pulmonary hypoplasia has been reported [6].

Kidneys may be dysplastic (82 %), absent (50%) or hydronephrotic. Other anomalies include hydroureter, urethral agenesis and megacolon [2-4]. Vaginal atresia or uterine anomalies like septate or bicornuate uterus are commonly associated [7,8]. But ovaries have been normal in all patients except in one [9]. The infrequent occurrence of distended bladder and abdomen can be attributed to the presence of vesicovagino-rectal fistulas through which fetal urine is passed into the vagina and/or rectum where it is reabsorbed [8]. Other associated anomalies are vertebral anomalies (56%), sacral agenesis or hypoplasia (47%), limb anomalies (25%), cardiac anomalies

(16%), tracheoesophageal fistula (18%) and single umbilical artery (37%) [4].

It is rare that the urinary bladder cannot be visualized due to associated renal agenesis or dysplastic kidneys. In the present case, there was no bladder distension or abdominal distension. EA+TOF, cardiac anomalies, cervical vertebral anomalies, partial sacral agenesis were the associated mesodermal anomalies. EA+TOF was reported in one previous case only [9]. Child did not survive long enough to perform detailed investigations including scans and karyotyping. Autopsy, solely for scientific research is not allowed in this Islamic country, and so was not performed. Embryologically cloaca is divided into anterior primitive urogenital sinus and posterior anorectal canal by cephalocaudal growth of mesodermal urorectal septum (URS) at 4 to 6 weeks of intrauterine life. This URS normally fuses with cloacal membrane dividing it into an anterior urogenital membrane and a posterior anal membrane. These 2 membranes rupture in the seventh week to form the external urogenital sinus and the anus. The point of fusion between URS and cloacal membrane becomes the perineum. In males, the primitive urogenital sinus develops into the bladder, the pelvic urethra, and the penile urethra. In females, it develops into the bladder, the membranous urethra, and the vestibule of vagina [3]. Failure of migration and/or fusion of the urorectal septum with the cloacal membrane during the first 50 days of gestation causes persistence of the cloacal cavity, cloacal membrane and failure of normal differentiation of external genitalia with absent perineal openings [3,8]. Abnormalities of cloacal septation, affect the formation of urogenital sinus and subsequently the normal development of Müller's tubercle from müllerian ducts and thus the development of

vagina and uterus [8]. Escobar studied their 6 cases and 11 previously reported cases. He named this entity as urorectal septum malformation sequence (URSMS) [8]. The spectrum of defects resulting from abnormalities of migration and differentiation of mesoderm in caudal developmental fold is “caudal dysgenesis spectrum”.

URSMS is an entity under this spectrum. Partial URSMS consists of a single perineal/anal opening that drains a common cloaca and absent anus [10]. Pauli and Bargaje prefer the term “lower mesodermal defects sequence” [3]. There is another theory in which a shift or rotation of the dorsal cloaca was important in the process of cloacal differentiation, and role of the urorectal septum is very minor. This shift brings the dorsal cloaca down to the area of the tail groove, thus establishing a future anal opening there. As the mesenchyme surrounding the cloaca grows, the cloaca becomes relatively smaller [4]. CDS is a result of a primary abnormality of “tail” development [4]. Possible etiologies are exposure to doxylamine succinate [3], aberrant migration of axial mesoderm in caudal region [3], genetic abnormality (isochromosome 18q), twinning, possibly owing to an insufficient number of cells in the gastrulation stage to populate 2 separate embryos, [5] selective damage to the lower end of the mesoderm by ochratoxin A (a fungal toxin) and etretinate (a retinoic acid derivative), and autosomal dominant inheritance [4]. EA+TOF is caused by defective mesenchymal tracheoesophageal septum (TES) in dividing the foregut into trachea and esophagus at 4-6 weeks of development [11,12]. It is possible that the same etiological insult which affected the URS, simultaneously harmed the TES also, which resulted in association of URSMS with EA+TOF in the present case. In fact the same

insult might have afflicted all the associated mesodermal anomalies.

Cloacal dysgenesis sequence is one of the many causes of stillbirth and immediate neonatal death or had termination of pregnancy, and only a few were born alive and died in the neonatal period [3]. With no egress of urine, infants have renal insufficiency caused by high pressure in urinary system and pulmonary hypoplasia causing pulmonary insufficiency from severe oligohydramnios, usually making CDS lethal [2,3,5,7,13]. Five cases of CDS survived and growing over the age of 1 year have been reported. One of these received renal transplantation for renal failure. The important common finding of these cases was the presence of urinary passage, such as patent urachus, vesicocolonic fistula, or vesico-amniotic shunting, partial disruption of the bladder that prevented renal deterioration, significant oligohydramnios and severe pulmonary hypoplasia. The other case was spared of the effects of oligohydramnios by the presence of a twin [2,5,7]. Long-term survivor is currently 12 years old. In the fetal period, she received a timely placement of vesico-amniotic shunt for a megabladder due to a severe urethral obstruction? urethral atresia. At birth, she had typical perineum of CDS. Vesicostomy and colostomy were performed. Anorectal and urogenital reconstruction were done at different ages [7]. CDS was considered not amenable to intrauterine interventions like vesicoamniotic shunts. Termination of pregnancy was recommended in the past, but in the light of reported occasional survivors, fetal vesicoamniotic shunt must be considered. Cloacal dysgenesis sequence can be diagnosed prenatally by ultrasound. Ultrasound findings include megacystis, oligohydramnios, perineal mass, hydronephrotic or dysplastic kidney, intracolonic calcifications due to calcified

meconium, nonvisualisation of bladder, dilated gut-loops, etc., [4,14]. CDS should be suspected in fetal obstructive uropathy (FOU) with absence of a keyhole sign in whom karyotype is male and sonography reveals colonic calcifications or abnormal phallic development [1,4,13,15]. The absence of anal, genital, and urinary openings with smooth perineum were common findings in males and females as per Sahinoglu [13]. Prenatal differential diagnosis of CDS consist of other FOU and persistent cloaca [3]. Fetal MRI [16] and fetal magnetic resonance urography at 18 weeks of gestation are more useful in diagnosis [17].

Conclusion

A case of CDS which was not suspected and not diagnosed antenatally, and which was born alive and died after 16h is reported. Sex was not detected. Child had no urinary bladder distension, but had associated EA+TOF, vertebral anomalies, and congenital heart disease.

Compliance with ethical statements

Conflicts of Interest: None.

Financial disclosure: None.

Consent: All photos were taken with parental consent.

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