Pathologic Quiz Case

Multiple Congenital Birth Defects in a Full-Term Infant

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A full-term, apparently male infant was born via normal spontaneous vaginal delivery to a healthy, 25-year-old white woman. The infant's Apgar scores were poor at birth (2, 1, and 1), and he died 15 minutes thereafter. Ultrasonography performed at 18 weeks' gestation had shown multiple anomalies. An abdominal magnetic resonance image performed on the mother at 25 weeks' gestation showed severe hydronephrosis of the right kidney (Figure 1, arrows). The patient's course was subsequently uneventful, except for severe oligohydramnios, which prohibited amniocentesis and fetal karyotyping. The family granted an unrestricted autopsy, which was performed soon after the baby's death.

The autopsy examination demonstrated a term baby (2.43 kg) with multiple congenital birth defects. Externally, there were multiple dystrophic features, including a mild Potter facies (low-set ears, prominent epicanthal folds, and receding chin), bilateral positional deformity of the lower extremities and bilateral club feet, ambiguous genitalia with a phalluslike structure and fused labia (Figure 2, arrow); and an imperforate anus (Figure 3, arrow). On internal examination, we noted bilateral small hypoplastic lungs (total weight, 13.5 g); a large atrial septal defect and aortic arch malformation; bilateral dysplastic horseshoe kidneys; severely malformed urogenital tract with barely recognizable structures of ureters, urinary bladder, urethra, and uterus; bilateral cystic gonads microscopically identified as ovaries; and deformed vertebrae (T12–L5). The placenta was grossly normal, with 3 vessels in the umbilical cord. Postnatal cytogenetic analysis demonstrated a normal female karyotype, 46,XX (Figure 4).

What is your diagnosis?

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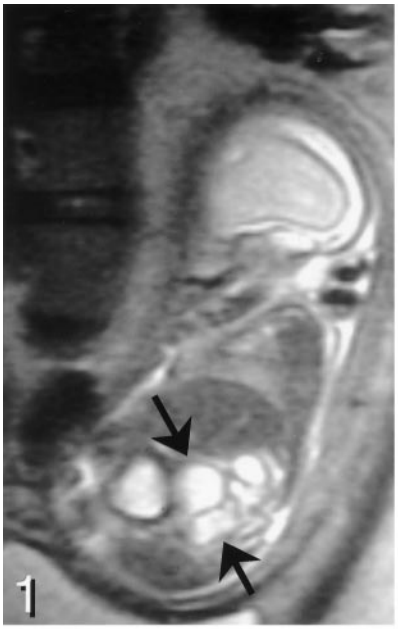

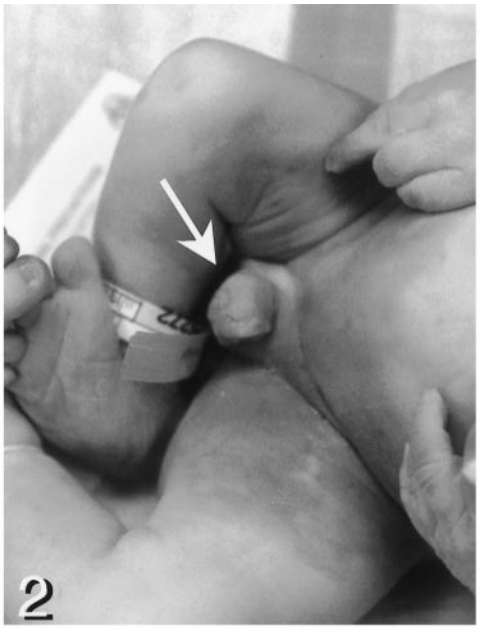

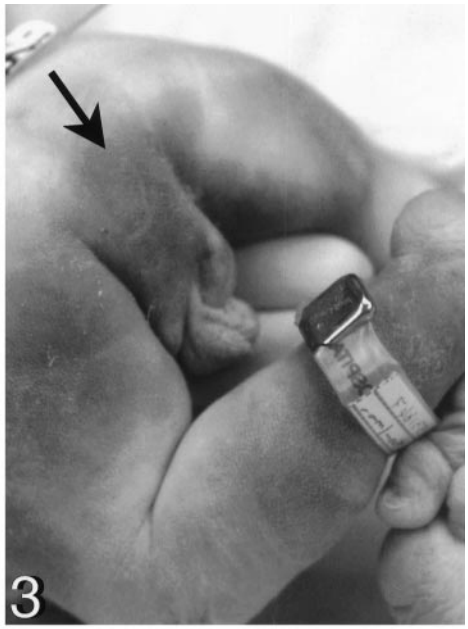

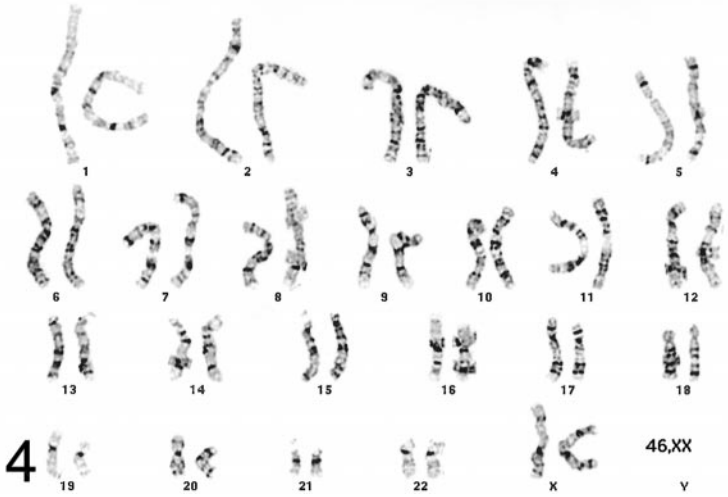

Pathologic Diagnosis: Urorectal Septum Malformation Sequence

The karyotypically normal female infant described here exhibits a specific pattern of developmental abnormalities with striking ambiguity of external and internal genitalia and associated multiple organ anomalies. The differential diagnoses include Potter syndrome, autosomal recessive polycystic kidney disease, VATER association, and urorectal septum malformation (URSM) sequence. In Potter syndrome, the primary defect is renal failure that occurs before an infant is born, either from bilateral renal agenesis or from other diseases of the kidney resulting in the lack of amniotic fluid (oligohydramnios). The typical features include Potter facies (widely separated eyes with epicanthal folds, broad nasal bridge, low-set ears, and receding chin) and positional deformities of the lower limbs with clubfeet. Oligohydramnios also stops development of the lungs and causes pulmonary hypoplasia. Autosomal recessive polycystic kidney disease is a rare genetic disorder. The classic presentation is an infant with oligohydramnios (Potter sequence); massively enlarged, symmetric, reniform kidneys; and pulmonary hypoplasia. Death usually occurs in the perinatal period. The term *VATER association* is noted by Quan and Smith[1] and is used to represent the association of vertebral defects, anal atresia, tracheoesophageal fistula, esophageal atresia, and radial and renal abnormalities. Cardiac defects, a single umbilical artery, and prenatal growth deficiency were included by Temtamy and Miller.[2]

Urorectal septum malformation sequence is a rare congenital malformation. Escobar et al[3] first designated the name and described the pathogenesis of this disorder. The typical features of URSM sequence are ambiguous external genitalia, disordered/malformed internal genitalia, and imperforate anus, vagina, and urethra. Other associated abnormalities include renal agenesis or dysplasia, pulmonary hypoplasia, congenital heart defects, and vertebral anomalies. It is found almost exclusively in females with a normal 46,XX karyotype.[3–7]

Wheeler and Weaver[8] further described partial URSM sequence and defined diagnostic criteria. This disorder represents a milder expression of the URSM sequence and is defined as a single perineal/anal opening that drains a common cloaca in combination with an absent (imperforate) anus and is associated with a variety of unusual malformations of the external genitalia.

The female infant we describe shared many features with each mentioned syndrome. The distinct abnormalities of the external and internal genitalia, however, are not typically found as part of features in Potter syndrome, autosomal recessive polycystic kidney disease, or VATER association, but are the major features of URSM sequence. Therefore, the diagnosis is most compatible with URSM sequence.

The pathogenesis of the partial and full URSM sequence is an abnormality in the septation of the primitive urorectal septum.[1,8] Normally by the sixth week of intrauterine development, the urorectal septum fuses with the cloacal membrane, dividing the cloacal cavity into a urogenital sinus anteriorly and a rectum posteriorly. The cloacal membrane then breaks down, leaving both a urogenital sinus and a rectum, which are open to the outside. Failure of this urorectal septum to divide the cloaca and/or approach the cloacal membrane leads in a cascading fashion to the URSM sequence, which blocks subsequent normal development of the internal and external genitalia, as well as the kidneys and urinary tract. Furthermore, some authors believe the URSM sequence might be a specific subset of lower mesodermal defects.[8] Patients with either full or partial URSM sequence are also at increased risk for sacral or other vertebral bone anomalies, tethered spinal cords, and congenital heart defects. With the full URSM sequence, patients usually die in the neonatal period of pulmonary hypoplasia. Children with the partial (milder form) URSM sequence tend to have less severe renal and internal genital anomalies and may have a better prognosis for long-term survival following appropriate surgical management.

To date, none of the cases reported with the partial or the full URSM sequence has shown a recurrence in siblings or offspring. Some authors[8] believe that the majority of urorectal septal defects are due to either new dominant gene mutations or possible teratogen exposure.

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