Infant of a Diabetic Mother With an Anomaly

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THE CASE

On initial examination, a male newborn has the finding shown in Fig 1.

Prenatal and Birth Histories

- Born to a 43-year-old gravida 5, para 4 woman with history of 1 abortion in the past.
- Pregnancy was complicated by advanced maternal age, chronic hypertension, obesity, and type 2 diabetes treated with insulin.
- Estimated gestational age: 39 weeks.
- Artificial rupture of membranes occurred 11 hours before delivery with clear amniotic fluid.
- Prenatal laboratory findings: Group B Streptococcus negative; hepatitis B surface antigen negative; human immunodeficiency virus negative; syphilis IgG antibody negative; Chlamydia trachomatis negative; Neisseria gonorrhoeae negative.
- Apgar scores: 3 and 7 at 1 minute and 5 minutes, respectively.
- At birth, the infant was noted to have respiratory distress and placed on continuous positive airway pressure. Physical examination at birth revealed an imperforate anus. An orogastric tube was placed to decompress his stomach. The infant was then transported to the NICU.

Presentation (Day 1)

The infant was placed nil per OS (NPO) and a large-bore nasogastric tube was placed to low-intermittent suction to decompress the stomach. Total parenteral nutrition was initiated for nutritional support. His glucose levels were monitored and found to be normal. The pediatric surgical team was consulted. Vital signs were as follows:

- Heart rate: 152 beats/min
- Respiratory rate: 65 breaths/min
- Blood pressure: 92/47 (mean 58) mm Hg
- Oxygen saturation: 95% (room air)
- Temperature: 99°F (37.2°C)

Physical Examination (Day 1)

- Birthweight = 4,660 g (99th percentile); occipital-frontal circumference = 35 cm (65th percentile); length = 52 cm (84th percentile).
- Head: Nares patent, palate intact, oral mucosa moist, anterior fontanelle soft, ears normally set and rotated.

AUTHOR DISCLOSURE

Drs Ball, Pimpalwar, and Vachharajani have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.
• Neck: Supple, full range of motion, clavicles intact.
• Lungs: Grunting, subcostal and intercostal retractions, and coarse lung sounds bilaterally.
• Cardiovascular: Regular heart rate, S1 and S2 normal, normal rhythm, good pulses equal in all extremities, capillary refill time 2 seconds
• Abdomen: Soft, nontender, nondistended, normal bowel sounds, no organomegaly, 3-vessel umbilical cord.
• Genitourinary: Testes descended bilaterally, bifid scrotum, imperforate anus, flat perineum
• Skeletal: Normal range of motion at all joints, no hip click, left first phalange with ulnar deviation (Fig 2), bilateral flat feet (Fig 3)
• Skin: No rash
• Neurologic: Response to stimulation present; pupils are equal, round, and reactive to light, with normal conjunctiva; red reflex bilaterally present

PROGRESSION

A chest radiograph obtained on admission to the NICU revealed retained lung fluid. On the day of birth, renal and head ultrasonography scans were normal. A prone cross-table lateral radiograph was obtained at 24 hours of age (Fig 4). Later that day, a colostomy and mucous fistula were placed to relieve intestinal obstruction caused by the imperforate anus.

At 2 days of age, the infant was noted to have decreased urinary output and an indwelling urinary catheter was placed. It was observed that he only produced urine when he cried, when his knees were brought to his chest, or when he was upset. The urinary catheter was removed at 3 days of age when he was noted to have spontaneous urination.

Further evaluation at age 3 days included a skeletal survey, revealing only 4 sacral vertebrae and an absent coccyx (Fig 5). A spinal ultrasound scan was also obtained, which revealed lack of movement of the conus medullaris and filum terminale with breathing, raising the possibility of a tethered spinal cord.

At 4 days of age, the nurse brought a diaper with urine mixed with meconium (Fig 6). A voiding cystourethrogram was obtained at 6 days of age with no evidence of vesicoureteric reflux or rectourethral fistula, but with a large amount of postvoid residual urine. Because of the association of sacral dysgenesis with neurogenic bladder, his postvoid
residual urine volume was monitored; however, monitoring was discontinued when the infant's residual urine volume was less than 10 mL per catheterization.

At 10 days of age, the infant developed *Escherichia coli* bacteremia and was treated with intravenous ampicillin for 10 days. At 29 days of age, he underwent a posterior sagittal anorectoplasty, and a rectoprostatic urethral fistula was diagnosed and repaired. A colostogram obtained during the procedure demonstrates the fistula (Fig 7).

Postoperatively, he was allowed to feed orally and was discharged at 45 days of age, with a discharge weight of 5,250 g; he was taking all of his feeding volume of 20 cal/oz by mouth. The ileostomy was closed 1 month later and rectal dilations were planned on subsequent follow-up.

Other testing included a microarray that did not detect any copy number changes of known clinical significance. The patient also had a *SALL1* and *SALL4* mutation analysis, result of which was negative. A limb reduction sequencing panel was heterozygously positive for *RAD1*.

**DIFFERENTIAL DIAGNOSIS**

Imperforate anus (high versus low) and 1 of the following:
- Diabetic embryopathy
- Townes-Brocks syndrome
- Vertebral, anorectal, cardiac, tracheoesophageal fistula, renal and limb (VACTERL) association
- Unknown association/syndrome

**ACTUAL DIAGNOSIS**

High imperforate anus and possibility of diabetic embryopathy or unknown genetic condition.

The imperforate anus was highly suspected on initial examination because of the lack of perineal contour (ie, flat perineum). There was no visible membrane on the perineum to suggest a low imperforate anus. Using the prone cross-table lateral radiograph, the distance between the putative anal opening and the lowest level (in this case, the highest level of the bowel gas) was measured and found to be 47.3 mm (Fig 8). Anecdotally, if this distance is over 20 mm, the defect is considered high. The highest level of the gas shown in the radiograph is above the putative coccyx and hence, a high imperforate anus is suspected.

**WHAT THE EXPERTS SAY**

The incidence of anorectal malformations ranges between 1 in 3,000 and 1 in 5,000 live births, with imperforate anus being associated with several syndromes. Anorectal malformations develop because of deranged embryologic development. Normally, the hindgut develops an anterior outpouching, which is the primitive bladder. The cloaca is the junction of the primitive bladder, also known as the allantois, and the hindgut. It is a common chamber where the genital, urinary, and intestinal tubes empty. The membrane covering the cloaca is the cloacal membrane. The cloaca is then divided by the urorectal septum into the anterior urogenital sinus and posterior anorectal canal. The posterior part of the cloacal membrane covers the future...
anus and failure of this membrane to open results in imperforate anus. The entire development occurs between 4 and 6 weeks of embryonic development. (1) Failure of any step in the developmental process results in a variety of anorectal and urogenital malformations. Anorectal malformations are often associated with many anomalies (Table).

Figure 9 summarizes the management approach for an infant with an anorectal malformation. The first step in the evaluation is a thorough physical examination with a focus on the perineum. The infant should be made NPO and started on intravenous fluid support and antibiotics. A nasogastric tube placed on low continuous suction will help to decompress the stomach and prevent emesis and aspiration. The infant should be inspected for associated malformations and evaluated radiographically for VACTERL association with a skeletal survey, renal ultrasonography, and echocardiography. A possibility of a tracheoesophageal fistula should be assessed by passing a nasogastric tube into the stomach.

The next step is to wait for 24 hours to characterize the level of the defect as high versus low. The radiographs obtained in the prone position are deferred for 24 hours because prior to that time, the rectum is collapsed by the surrounding sphincters and would not reveal the correct level of the defect. Early imaging can lead to a false-positive diagnosis of a high rectum. The need for a colostomy is deferred for 24 hours because significant pressure in the lumen of the rectum is required to force meconium through a fistula. Meconium on the perineum is a sign of a recto-perineal fistula, and hence, points to the presence of a distal rectum. This confirms the diagnosis of a low imperforate anus and that a colostomy is not indicated. Presence of meconium in the urine is a sign of rectourinary fistula, which indicates a high-level imperforate anus. The lack of contour to the perineum is a sign of high imperforate anus. A distance of more than 20 mm between the probe on the putative anal opening and the highest level of gas in the rectum is a sign of a high-level imperforate anus. Alternatively, visualization of air below the coccyx is consistent with a low-level imperforate anus. (2)

Anoplasty can be performed in low-level imperforate anus if air is visualized above the coccyx. A posterior sagittal repair with or without a preceding colostomy is performed if the air is visualized above the coccyx. A preceding colostomy before definitive repair allows the anatomy to be further delineated by colostogram before definitive repair is undertaken.

Long-term outcomes after treatment of an infant with an imperforate anus are variable. Constipation occurs more commonly in neonates with a low imperforate anus. Incontinence of the rectum with diarrhea is noted in 75% of affected neonates with a high imperforate anus.
Constipation and incontinence can be managed using multiple strategies. (3)

VACTERL association was ruled out in this case because there was no tracheoesophageal fistula and the patient’s echocardiography and renal ultrasonography results were normal. Ulnar deviation of the thumb was noted, but the rest of the skeletal survey results were normal, except for the sacral dysgenesis. There are no confirmatory genetic tests for VACTERL association.

Townes-Brocks syndrome was first described in 1972. (4) The disorder is characterized by an autosomal dominant inheritance pattern, noted with the detection of mutations in the SALL1 and SALL4 genes. Marked variation in the severity of expression has been described. It is associated with various anomalies of different organ systems. Craniofacial abnormalities can include auricular anomalies such as ear tags or overfolding of the helices and also hemifacial microsomia. Abnormalities in hearing, including sensorineural hearing loss, have been described and can be progressive over time. Anomalies of the limbs often involve the thumbs, which are noted to be bifid or triphalangeal or have ulnar deviation. There is often fusion or absence of the metatarsals, absent or hypoplastic third toe, or clinodactyly of the fifth toe. Imperforate anus is often associated with Townes-Brocks syndrome, along with rectovaginal and rectoperineal fistulas. Multiple genitourinary malformations are also associated with the syndrome such as hypoplastic kidneys, renal agenesis, posterior urethral valves, vesicoureteral reflux, and meatal stenosis. (4) Townes-Brocks syndrome is often associated with some other occasional abnormalities such as bifid scrotum, scoliosis, prominent perineal raphe, abnormalities of the toes, microcephaly, and microtia.

### TABLE. Common Anomalies Associated With Anorectal Malformations

<table>
<thead>
<tr>
<th>GENITOURINARY 33%–50%</th>
<th>CARDIOVASCULAR 33%</th>
<th>GASTROINTESTINAL</th>
<th>CENTRAL NERVOUS SYSTEM</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicoureteral reflux</td>
<td>Tetralogy of Fallot</td>
<td>Esophageal atresia + tracheoesophageal fistula</td>
<td>Spina bifida</td>
<td>Presacral masses</td>
</tr>
<tr>
<td>Renal agenesis</td>
<td>Ventricular septal defect</td>
<td>Duodenal atresia</td>
<td>Tethered cord (25% of patients with anorectal malformations)</td>
<td>Lipoma</td>
</tr>
<tr>
<td>Renal dysplasia</td>
<td>Transposition of the great vessels</td>
<td>Malrotation</td>
<td>Meningocele</td>
<td>Dermoid</td>
</tr>
<tr>
<td>Ureteral duplication</td>
<td>Hypoplastic left heart syndrome</td>
<td>Hirschsprung disease</td>
<td>Spinal dysraphism</td>
<td>Teratoma</td>
</tr>
</tbody>
</table>

among others. (4) Townes-Brocks syndrome was a possibility in this case because of the presence of the imperforate anus, bifid scrotum, abnormal thumb (Fig 3), and flat feet (Fig 4). However, SALL1 and SALL4 mutation analysis, which confirms the diagnosis, was negative.

Diabetic embryopathy ([https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=1926]) is the most likely possibility because the neonate’s mother had diabetes, he was large for gestational age at birth, and he had respiratory distress syndrome at birth. He also had sacral dysgenesis. However, the neonate did not have hypoglycemia, hypocalcemia, hypertrophic cardiomyopathy, or signs of caudal regression syndrome (he had good muscle bulk in the legs and normal spine except for the sacral anomalies).

The significance of the heterozygote-positive RAD1 testing that was part of a limb reduction sequencing panel is unknown. Perhaps this infant has a genetic abnormality that has not yet been identified.

**References**


**Suggested Readings**


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