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Pathology of cloaca anomalies with case correlation

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ABSTRACT

During the fourth week of human embryo development, a transient common channel known as a cloaca is formed from which three cavities with three external orifices arises. Cloaca anomalies occur when there is failure of separation of the rectum, vagina, and urethra channel resulting in a single drain into the perineum. In our previous institutional studies, Runck et al.[1] compared human and mouse cloaca development and found early mis-patterning of the embryonic cloaca deranged hedgehog and bone morphogenetic proteins (BMP) signaling. Also, our group reported the embryological correlation of the epithelial and stromal histology found in step sections of the common channel in 14 cloaca malformations in humans.[2] In this review, we present the pathology of a 4-year-old female with a cloaca and VACTERL complex, and summarize our current knowledge of cloaca pathology. Furthermore, we suggest that careful pathological examination of cloaca specimens in conjunction with surgical orientation may result in a better understanding of the etiology of this condition.

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Cloaca anomaly (CA) is the most complex and severe form of anorectal and urogenital malformation in females.[3] Approximately, 1 in every 20,000 live births has CA.[4,5] Cloaca is a transient embryonic cavity which is subsequently divided by the urorectal septum into the urogenital sinus (ventral) and hindgut (dorsal). Eventually, the common channel then divides into separate rectum, vaginal, and urethra structures with three separate external openings.

Persistence of the common channel occurs in 90% of all CA. There is failure of separation resulting in drainage of urine, stool, and vaginal secretions via a single common channel into the perineum (Figure 1A and B). Upon evaluation, the common channel mucosa may resemble bladder or vaginal mucosa (Figure 1C), or colonic mucosa (Figure 1D). Endoscopically, CA can be categorized by the length of the common channel which ranges from 1 to 10 cm. The overall outcome of these patients is dependent on the quality of sacrum and length of the common channel. If the common channel is longer than 3 cm, the greater the likely hood of poor bowel control, neurogenic bladder, and reproductive abnormalities.[6]

The external genitalia in CA often appears small. In 40% of the cases, abdominal examination may reveal a mass which likely represents a distended vagina also known as hydrocolpos.[7] CA may occur as part of caudal regression syndrome. Cloacal exstrophy[8] occurs in 1 per 100,000 live births, and differs from a CA in that there is an anterior abdominal wall defect in which two hemi-bladders are visible and are separated by a midline intestinal plate, an omphalocele, and an imperforate anus.

In this review, we summarize our current knowledge of cloaca pathology through a case presentation of a 4-year-old patient with a cloaca anomaly associated with VACTERL complex who underwent a posterior sagittal anorectovagino-urethroplasty (PSARVUP) at our institution.

Case presentation

A 4-year-old female thought to possibly have a long common channel (Figure 2A), had a single perineal opening (Figure 2B), and VACTERAL. She underwent a colostomy shortly after birth and presented to our institution for repair. Rotational scan of the operative field (Figure 2C) showed a long common channel and a vaginal pouch posterior and inferior to the bladder. Figure 2D shows a MRI of the spine with tethered cord. Operative findings included the following: (1) 3.5 cm long common channel; (2) right blind vaginal pouch measuring 1.5 × 1.0 cm^2 just posterior and inferior to the urinary bladder; (3) left ureteral opening into the common channel; (4) atretic left Mullerian structure (Figure 2E); and (5) blind ending right Mullerian structure with no evidence of a well-developed cervix. Multiple specimens were excised and sent to pathology. The original colostomy was brought

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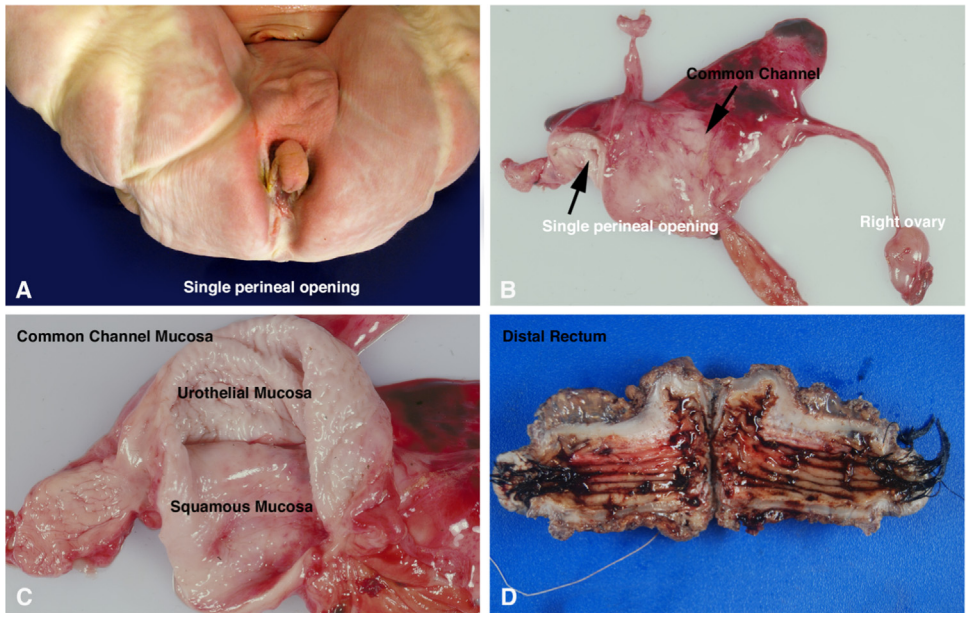

Fig. 1. Various cloaca anomalies. (A) External examination demonstrates fused labia and single perineal opening. (B) Block dissection demonstrates a common channel between bladder, rectum, and vagina. (C) The common channel mucosa may resemble bladder mucosa, vaginal mucosa, or (D) colonic mucosa.

down to become the neo-vagina and the remaining colon was resected, to further create three orifices (Figure 2F).

The left Mullerian remnant was composed of 1.2 cm fallopian tube and 1.6 cm fibrous cord. Histology demonstrated cross-section of a fallopian tube normally lined by ciliated columnar epithelium, and a fibrous cord composed of smooth muscle (Figure 3A). The 1.7 g, 3.8 × 0.8 × 0.3 cm^3 right Mullerian remnant (Figure 3B) was composed of a hypoplastic uterus with a well-defined endometrial cavity with inactive endometrial glands and stroma. The attached fallopian tube has preserved architecture. Although hypoplastic, the myometrium demonstrated normal histology (Figure 3C). Cervical and vaginal mucosa was absent. The excised blind 1.5 × 0.9 cm^2 vaginal pouch was composed of nonkeratinizing metaplastic squamous epithelium with occasional cells exhibiting Mullerian-type epithelium surrounded by chronic inflammation (Figure 3D and E). The rectum specimen was composed of two longitudinal pieces of partially cauterized red-tan mucosa measuring 1.8 × 1.2 × 0.6 cm^3 and 1.2 × 1.1 × 0.8 cm^3. Histology showed widely spaced haphazardly arranged crypts with mostly denuded patches of anal transitional zone epithelium with columnar surface cells and scanty mucin production (Figure 3F) on the surface. Muscularis mucosa and propria smooth muscle fibers were disorganized. Proximal and distal colostomy and colon resection specimen demonstrated normal morphology.

Normal human embryology and histology

The entrance of the mesonephric duct into the primitive urogenital sinus occurs at 4–6 weeks gestation. This duct is a landmark distinguishing the cephalad vesicourethral canal which gives rise to the bladder and pelvic urethra, and the caudal urogenital sinus which gives rise to the distal vaginal vestibule.[9] At the end of the first month of gestation, mammals' embryos develop separate anorectal and urogenital canals by septation of the common channel.[9–11] There is massive epithelial apoptosis of the urorectal septum, fusion of the epithelial walls of the cloaca, and simultaneous active growth of the mesenchyme within the urorectal septum.[12] The common channel is lined by endoderm derived mucosa overlying mesoderm. The anal canal, vaginal, and urethral openings are established by the end of the first trimester.

Histologic examination showed differentiating colonic mucosa from small intestinal mucosa becomes difficult prior to 16 weeks gestation. Subsequently, goblet cells and crypts of Lieberkuhn develop. Ganglion cells appear around 21 weeks, and between 30 and 40 weeks the villi disappear and muscle layers are entirely developed. During the middle to end of the third trimester, the anal canal is now lined by mature squamous epithelium. The anal transitional zone epithelium is stratified cuboidal to columnar with scattered goblet cells and peg cells on surface, which is different from adjacent colonic mucosa. At term, the urethra is lined by mature urothelium as it exits the bladder (proximal), pseudostratified and stratified columnar epithelium (midportion), and stratified squamous cells near the external urethral orifice (distal). Müllerian epithelium of the vaginal canal is replaced by stratified mature pre-pubertal squamous mucosa by 18–20th week of gestation. By 32 weeks, there is discrete layering of the lamina propria, muscularis mucosa, and outer/inner smooth muscle layers of the muscularis propria.[13–15] Although the urethra, vagina, and colon all arise from a common channel, they are functionally and morphologically different. The definitive molecular and morphogenetic mechanisms that give rise to these different epithelial surfaces still remain a mystery.

Pathogenesis of cloaca anomalies

Owing to the inability to directly investigate human embryonic cloaca development, research has heavily relied on the use of animal models for CA. The spectrum of anomalies is suggested to be dependent on the stage of embryological developmental arrest.[16,17] Several animal and few human embryo models[1,18–36] have speculated the pathogenesis of CA may be the results of disruption in patterning, cell division, and cell polarity secondary to disruption of signaling paracrine factors and genes.

Cloacal septation depends on epithelial to mesenchymal signaling mediated by Sonic Hedgehog (*Shh*)[1,18–24] or its downstream mediators, *Gli2*, and *Gli3*,[25,26] from the cloacal endoderm which disrupts cell indentification, proliferation, and survival mechanisms. Previously, members of our group, Runck et al.,[1] did