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Case Report

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Partial urorectal septum malformation sequence in a kitten with disorder of sexual development

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Abstract

A 2-month-old kitten exhibited simultaneously an imperforate anus, hypospadias, rectourethral fistula and genital dysgenesis (penis restricted to the glans, absence of prepuce and bifid scrotum). Surgical correction consisted of separation of the urinary and digestive tracts, perineal urethrostomy and connection of the rectum to the newly made anal opening. Pathological examination of the testes, conventionally removed at 9 months of age, showed no mature spermatozoa and underdevelopment of germ and Leydig cells. In humans, the absence of an anal opening in association with abnormal sexual development defines the urorectal septum malformation sequence. Here, we describe the first case of this syndrome in a kitten with a normal male karyotype (38,XY) and a normal coding sequence for the *SRY* gene. Both the rectourethral fistula and observed genital abnormalities might have been induced by a disturbance in the hedgehog signalling pathway. However, although four polymorphic sites were identified by *DHH* gene sequencing, none cosegregated with the malformation.

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Various disorders of sex development (DSD), although rare, have been described in cats, including true hermaphrodism[1,2] and pseudohermaphrodism.[3–6] In all the feline DSD cases described in the literature, abnormalities were restricted to genital tract development, while other systems, such as the digestive tract, were normal. Conversely, normal genital differentiation has been observed in the case of anorectal abnormalities.[7,8] In humans, abnormal sexual development and the absence of perineal openings are observed concurrently, and termed the urorectal septum malformation (URSM) sequence.[9] The presence of a single opening, draining a common cloaca, along with an absent (imperforate) anus, characterises a partial URSM (PURSM) sequence.[10] In human DSD nomenclature, URSM is classified as 'syndromic associations of male genital development (eg, cloacal anomalies, cryptorchidism, etc)'.[11] This report describes, for the first time, a case of PURSM in a kitten that simultaneously displayed DSD (38,XY; *SRY*-positive) and a single perineal opening, common to the digestive and genitourinary tracts.

This 2-month old Persian, presumed to be a female, was referred at the end of the weaning period for an imperforate anus. At the normal place of the anal opening, only a dimple was present. A single perineal orifice was draining both urine and faeces (Figure 1). Genital abnormalities described in association with PURSM in human males include hypospadias, phallic hypoplasia, penoscrotal transposition and bilateral undescended testes.[10] This kitten presented a large hypospadias and a penis restricted to the glans. The testes were palpable outside the inguinal ring at 2 months, but not in a definitive scrotal position. In other reports of kittens with rectogenital fistulae, no genital abnormalities have been described,[3–5] and the associated non-genital abnormalities, found exclusively in females, were mainly partial tail agenesis and,

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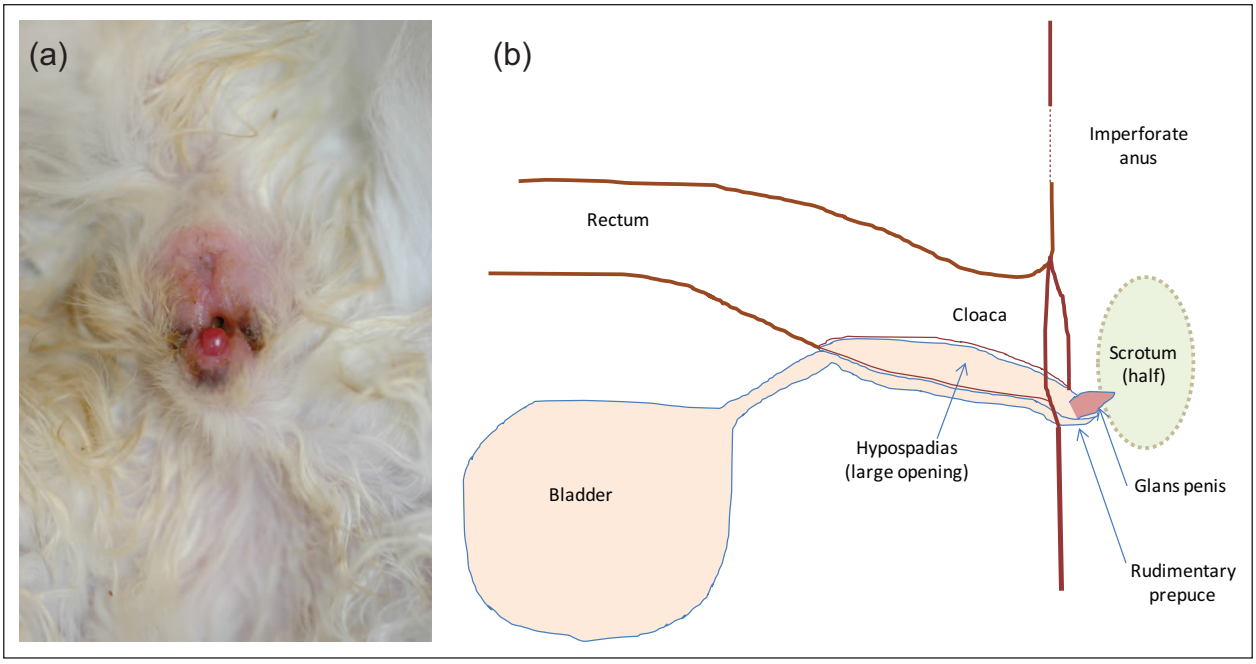

Figure 1 (a) Anogenital region of the kitten (in ventral recumbency) at 2 months of age. (b) Diagrammatic representation in a sagittal view. The imperforate anus is visible as a dimple. The urethra, dilated in its pelvic part, forms dorsally a hypospadias connecting with the rectum. A single-opening draining, a cloaca common to the digestive and urinary tracts, is apparent at a distance similar to the anogenital distance in females, between two scrotal pouches (testes were not in a definitive scrotal position at 2 months). The glans penis was congested and only a rudimentary prepuce was present

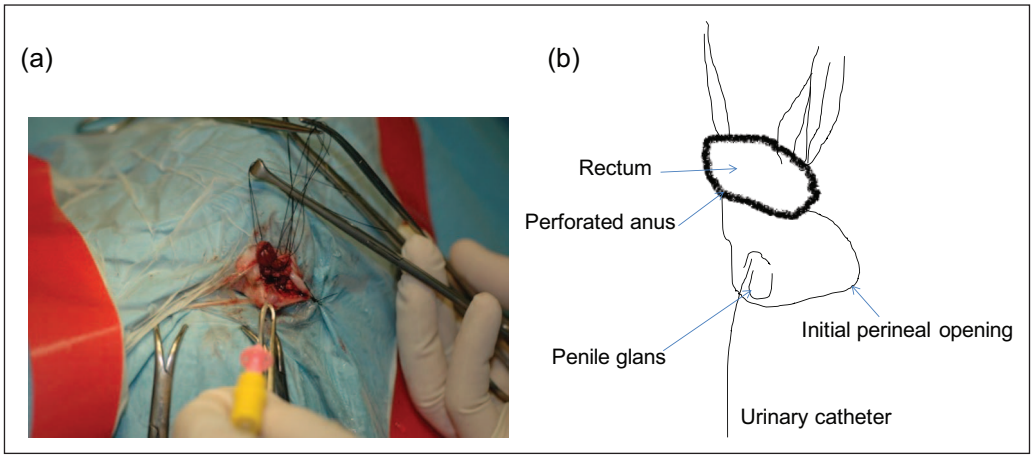

Figure 2 (a) Peroperative view of the perineal region of the kitten (in ventral recumbency) during surgical reconstruction. (b) Schematic representation of the anatomical structures

less frequently, umbilical hernia, cleft palate, sacrocaudal dysgenesis and hydrocephalus.[8] None of the large number of abnormalities associated with URSM in humans (vertebral, limb, cardiac, tracheoesophageal defects) was identified in this kitten. In particular, ultrasound examination did not reveal any of the renal abnormalities (agenesis, dysplasia, hydronephrosis) observed in up to 82% of affected infants.[9,10] Cytogenetic evaluation of in vitro-cultured lymphocytes revealed a normal, male chromosome complement (38,XY) (Supplementary Figure 1). The presence of the *SRY* gene was confirmed by polymerase chain reaction (1022 base pairs), with primers designed on the basis of the feline *SRY* gene sequence (Supplementary Figure 2). The earlier reported polymorphism (389G>C)[2] was not identified in this study, but two deletions in the 3′-flanking region of the *SRY* gene distinguished the *SRY* sequence of our kitten from the reference and control cat (Supplementary Figure 3).

The radiographic appearance and size of the colon were unremarkable, suggesting normal colonic motility. A

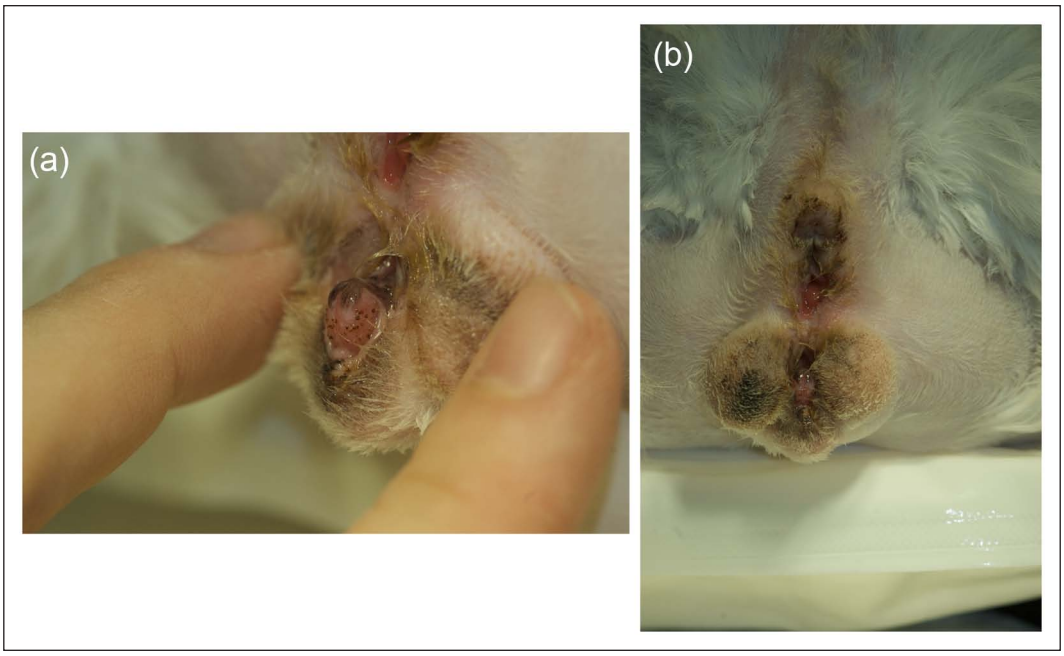

Figure 3 (a) Anogenital region of the cat (in ventral recumbency) at 9 months of age. A rudimentary prepuce can be observed, just behind the glans penis. Two openings have been reconstructed: above, the anal opening connecting the rectum; below, the opening of the perineal urethrostomy. (b) Closer view of the glans penis protruding through the perineal urethrostomy opening

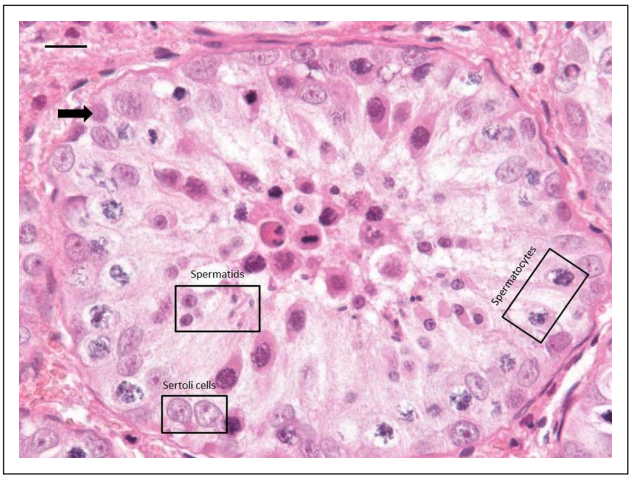

Figure 4 Histological view of a representative seminiferous tubule (haematoxylin–eosin–safran). Magnification 400×. Error bar = 15 µm. The number of germ cell layers appears abnormally low (black arrow); Sertoli cells, spermatocytes and spermatids (all indicated in the figure above corresponding boxes) are present, whereas mature spermatozoa are absent. Haematoxylin–eosin–safran stain. Bar = 15 µm

liquid diet was maintained until surgery, which consisted of perineal urethrostomy, reopening of the anus and connection of the rectum. After premedication (acepromazine, 0.05 mg/kg, IV; Calmivet, Vétoquinol), general anaesthesia was induced with propofol (6 mg/kg IV; Rapinovet, MSD) and maintained with isoflurane (Forene; Abbvie) in oxygen. Analgesics (0.1 mg/kg morphine sulfate IV; morphine chlorhydrate, Aguettant) and antibiotics (amoxicillin, 20 mg/kg, IV; Clamoxyl, Pfizer Santé Animale) were administered. The kitten was placed on a heating pad in ventral recumbency with its tail fixed over its back. The perineum was clipped and prepared for aseptic surgery. A midline dorsal incision of the perineal orifice, ending at the dorsal limit of the dimple, was performed. The external anal sphincter had been identified previously on the dorsal part of the incision. The rectourethral fistula connected the dorsal wall of a dilated urethra and the ventral portion of the terminal rectum. After fistula dissection, an incision was made to separate the urethra from the rectum. The rectal opening was carefully mobilised through the external anal sphincter (Figure 2) and sutured to the surrounding subcutaneous tissues with a simple continuous pattern of 4–0 polydioxanone sutures (PDS; Ethicon) and, finally, to the skin with simple interrupted sutures of 4–0 polyamide (Ethilon; Ethicon).[12] The urethral opening was sutured with 6–0 or 7–0 polydioxanone (PDS; Ethicon) simple interrupted sutures at the initial position of the perineal opening. The cutaneous incision was sutured with simple interrupted sutures of 4–0 polyamide (Ethilon; Ethicon).

One month after surgery, the kitten received a classical solid diet, and faecal elimination became normal after 2 months. Micturition and growth were normal. At the age of 9 months, the cat was of normal stature; a rudimentary prepuce was observed, just behind the penis glans protruding through the perineal urethrostomy orifice. Two testes were found in a bifid, but normally developed,

scrotum (Figure 3). The time of testicular descent could not be documented. After conventional removal, the testes were found to be abnormally small, but the epididymis was present. Overall, pathological examination of several sections of both testes revealed seminiferous tubules of small diameter lined by a small number of germ cells layers. The paucity of germ cells may reflect an abnormality of spermatogenesis, either primary or secondary to possible delayed testes descent or to URSM. Sertoli cells and the early stages of spermatogenesis (until elongated spermatids) were present, but no mature spermatozoa were observed (Figure 4) and Leydig cells were rare. Five years later, the animal is still alive and healthy.

Both abnormal development of the perineal region and testicular disorders can result from a disturbance of the hedgehog signalling pathway. Sonic hedgehog (*Shh*) and other members of the hedgehog family (*Gli2*, *Gli3*) are known to be involved in epithelio-mesenchymal interaction, which is critical for urorectal septum formation and closure,[13,14] whereas desert hedgehog (*Dhh*) is essential for Leydig cell development and linked to hypospadias.[14,15] Indeed, knockout *Dhh* male mice are sterile owing to the absence of mature spermatozoa.[16] Comparison of the *Dhh* gene sequence in this kitten and in five control male cats revealed only four common polymorphic sites (Supplementary Table 1) in exon 1 (deposited in GenBank: KF358988). None of them co-segregated with the malformation.

Conclusions

Newborn animals with discordant phenotypes regarding URMS within the same litters have been reported, for example, dizygous lambs[13] and human twins;[17] here, the littermates of the affected kitten were normal. This makes it unlikely that URSM is of teratogenic origin. Indeed, genetic analyses of porcine lineages, in which the incidence of atresia ani with rectogenital fistulas is high, suggest an oligogenic or a polygenic determinism for URMS.[18]

Supplementary data Supplementary data is available at http://jfm.sagepub.com/.

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