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A Case Report of Ovotesticular Disorder of Sex Development (OT-DSD) in a Baboon (*Papio* spp.) and a Brief Review of the Non-Human Primate Literature

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Abstract

Background—Disorders of sexual development are rare in non-human primates.

Methods—We report a case of true hermaphroditism in a 19-year-old, nulliparous, female baboon (*Papio* spp.)

Results—At necropsy, the animal was obese with adequate muscle mass and hydration. Reproductive organs appeared normal with the exception of two firm nodular structures in the myometrium (1–1.5 cm diameter) and a thickened, dark endocervical mucosa. Histologically, both gonads were ovotestes, and contained discrete areas of ovarian and testicular tissue. There were follicles in various stages of development surrounded by ovarian stroma. Other areas contained hypoplastic seminiferous tubules lined by Sertoli cells, but lacked germ cells and spermatozoa. The uterine lesions were consistent with adenomyosis and cystic endometrial hyperplasia. Cervical lesions were consistent with atypical glandular hyperplasia and squamous metaplasia with dysplasia.

Conclusion—We report the first case of ovotesticular disorder of sexual development (OT-DSD), or true hermaphroditism in a baboon.

Keywords

True hermaphrodite; Ovotestes; Adenomyosis

1. Introduction

Disorders of sexual development (DSD) is a general term used to describe a spectrum of developmental pathologies associated with defective gonadal differentiation, each with distinct pathogenesis arising from defects at different stages of the reproductive cycle (gametogenesis or embryogenesis) leading to one or more of the following alterations: abnormal karyotype, abnormal gonadal tissues, and ambiguous external and internal reproductive organs [1].

In humans, DSD are classified into three categories: 1) Sex chromosome disorders, which include 45, X Turner syndrome, 47, XXY Klinefelter syndrome, and chromosomal ovotesticular DSD, 2) 46, XY DSD, which include developmental testicular disorders and defects in androgen synthesis/action, and 3) 46, XX DSD, which include developmental ovarian disorders and fetal androgen excess [2]. This nomenclature is based on presence of sex chromosomes, genotype, gonadal composition, phenotype and cause of pathology, and has been adopted into human and veterinary use to replace ambiguous terminology such as “true hermaphrodite” and “pseudohermaphrodite” [3, 4].

Recently, ovotesticular DSD (OT-DSD), formerly known as true hermaphroditism, has been further sub-classified into 46,XY ovotesticular DSD, 46,XX ovotesticular DSD, and chromosomal ovotesticular DSD (46, XX/46, XY chimerism or 45, X/46, XY mosaic type) [2, 4]. OT-DSD describes a condition where there is presence of ovarian and testicular tissue either in the same gonad (ovotestes), or in the contralateral gonad [5]. The contralateral location of opposite ovary and testis is most common, followed by bilateral distribution, where both gonads are ovotestes, and unilateral distribution (rare), where one gonad is an ovotestes and the contralateral is a normal testes or ovary [4, 6]. The most commonly observed gonad in OT-DSD is the ovotestes with the presence of seminiferous tubules in the testicular tissue and follicles in the ovarian tissue [7, 8].

Disorders of sexual development are rare in non-human primates. There has been one reported case of a bilateral OT-DSD (ovotestes) in a 105 day-old female rhesus macaque [9]. X-monosomy with gonadal dysgenesis has been reported in a cynomolgus [10] and a rhesus macaque [11]. Klinefelter’s syndrome [12], Turner’s syndrome [13], XY-gonadal dysgenesis [14] and male pseudohermaphroditism [15] have been reported in baboons. There was also a report of a possible intersex baboon with the size and behavior of a male, but with macroscopic ovaries [16]. An XX/XY mosaic male chimpanzee and a suspected XX male hanuman langur monkey (*Presbytis entellus*) have also been reported [17, 18]. We report a case of OT-DSD in a 19 year old, female baboon (*Papio* spp.) that was identified as an incidental finding during a necropsy.

2. Materials and Methods

2.1 Animal

The 19-year old, colony born, nulliparous, female baboon was socially housed in outdoor metal and concrete gang cages, fed a commercial monkey diet (Teklad®, PMI Nutrition International, LLC, Brentwood, MO 63144) supplemented with grains, fruits and vegetables,

and provided water *ad libitum*. From 2009 to 2016, this animal was a part of the breeding colony. Between 1998 and 2016, the animal was assigned to six studies relating to diet and genetic effects on atherosclerosis, neuroimaging, epilepsy, and reproductive senescence. All animal care and procedures were approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee.

2.2 Pathology

The animal was euthanized for tissue collection. A complete necropsy was performed, and tissue samples were taken for histologic evaluation. All tissues were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut at 5 microns, stained with hematoxylin and eosin and evaluated by light microscopy by board-certified veterinary pathologists. For immunohistochemical labeling, reagents were procured from Ventana Medical Systems, Tucson, AZ, USA. All stains were completed using the Ventana BenchMark Ultra automatic stainer (Ventana Medical Systems, Inc., Tucson, AZ, USA) with the UltraView DAB detection kit (Ventana Medical Systems, Catalog number 760–500). Immunohistochemical labeling was performed on formalin-fixed, paraffin-embedded, 4 μ m thick sections of endocervix. Slides were deparaffinized and treated with heat induced epitope retrieval in cell conditioning solution-CC1 (Ventana Medical, Systems, Inc.) at 99°C for 36 minutes. Ki-67 rabbit anti-human monoclonal antibody (Ventana Medical Systems Catalog Number 790-4286) was applied for 48 minutes, or P16 mouse anti-human monoclonal antibody (Ventana Medical Systems Catalog Number #725-4713) was applied for 32 minutes. All slides were counterstained with haematoxylin (Ventana Medical Systems Catalog Number #760-2021)/bluing (Ventana Medical Systems Catalog Number #760-2037) for 4 minutes.

2.3 Hormonal Evaluation

Archived frozen serum samples were submitted for hormonal assays at the Endocrine Technologies Support Core (ETSC) at the Oregon National Primate Research Center (ONPRC) (<http://www.ohsu.edu/xd/research/centers-institutes/onprc/research-services/research-support/endocrine-technology.cfm>). Leutinizing hormone (LH) and follicle stimulating hormone (FSH) levels were tested using a direct iodination radioactive immunoassay and estradiol, progesterone, and testosterone levels were detected using a chemiluminescence assay on Roche Cobas e411 Automatic Clinical Platform (Roche Diagnostics). Anti-Mullerian hormone (AMH) and inhibin B levels were tested using the ELISA method, as per their standard protocols.

3. Results (Case Report)

3.1 Clinical and Reproductive History

The 19-year old, colony born, female baboon was nulliparous despite multiple breeding attempts. The available readings of the reproductive cycle during a 10 year period (2007 – 2017), which corresponded to biological age 10–19 years old, demonstrated an irregular late follicular phase, which corresponds to estrogen stimulation and +4 swelling (range 1–33 days), paralleled by a short early follicular phase (0–2 swelling) and periodic irregular bleeding (2–5 days). A prolonged luteal phase without menstrual bleeding was registered

two months after the animal was placed into a new breeding harem cage (12 years of age). Pregnancy color and delay of menstrual bleeding was detected once, followed by bleeding at estimated conception day 54 (13 years of age).

3.2 Gross Pathology

At necropsy, the animal had adequate muscle mass and hydration with excess adipose tissue. The uterine wall was deformed by two approximately 1–1.5 cm diameter, firm nodules. The endocervical mucosa was thickened and dark. Both gonads appeared to be grossly unremarkable ovaries.

3.3 Histology

Lesions were restricted to the reproductive tract. Histologically, both gonads were ovotestes, composed of discrete areas of approximately 70% ovarian and 30 % testicular tissue. (Figure. 1A). The ovarian tissue was composed of follicles in various stages of development surrounded by ovarian stroma (Figure 1B and 1C). The testicular tissue was composed of hypoplastic seminiferous tubules that were lined by Sertoli cells, but lacked germ cells and spermatozoa (Figure 1D). The myometrium was expanded by multifocal areas of adenomyosis, characterized by nests of well-differentiated uterine glands extending into the deep myometrium (Figure 2A). There was diffuse cystic endometrial hyperplasia with a hypercellular endometrium that multifocally contained ectatic glandular elements filled with eosinophilic fluid (Figure 2A). The changes in the endocervix were most consistent with squamous metaplasia and mild dysplasia (Figures 2B and C). The basal 2/3 of the epithelium was mostly composed of variably sized packets of densely packed epithelial cells separated by a fibrous stroma. In the superficial 1/3 of the mucosa, the epithelial cells generally appeared to have basilar nuclei and often formed cystic structures surrounding eosinophilic fluid. Epithelial cells in the endocervix, exhibited nuclear immunoreactivity for the proliferation marker Ki-67 (Figure 2D), however were negative for p16 (Figure 2E), a marker used to identify cervical malignancies in humans.

3.4 Hormonal Evaluation in Relation to Sex

The results of hormonal evaluation, performed on an archived serum sample taken during the period of pseudo-pregnancy and delay of menstrual bleeding (at 12 years of age), are presented on Table 1. The level of estrogen and progesterone were within, and the level of LH and FSH were below, the range for female baboons in the colony. Testosterone levels could not be compared due to the detection limit of the assay.

4. Discussion

Disorders of sex development occur in many species, however cases of OT-DSD remain a sporadic event across mammalian species [9]. OT-DSD is defined by the co-presence of both ovarian tissue containing follicles and testicular tissue containing seminiferous tubules. In addition, OT-DSD can be classified as contralateral (ovary + testes), bilateral (2 ovotestes), or unilateral (1 ovotestes + 1 ovary or 1 testicle) dependent on histopathologic evaluation of the gonads.

We report a case of bilateral OT-DSD in a phenotypically female baboon (*Papio* spp.) The baboon had fully developed female tubular genitalia with a uterus and an external vaginal opening, however, the animal was nulliparous despite multiple opportunities to breed. Both gonads were histologically confirmed as ovotestes, containing both ovarian follicles and seminiferous tubules. The uterine lesions (adenomyosis and cystic endometrial hyperplasia) and endocervical changes (atypical glandular hyperplasia and squamous metaplasia with dysplasia) were of uncertain significance. The endocervical lesions could be a pre-neoplastic change, as many hyperplastic endocervical glandular lesions overlap with early neoplastic lesions [19, 20]. The immunopositivity for Ki-67, a proliferation marker, and immunonegativity for p16, a marker used to identify cervical malignancies, is more consistent with a hyperplastic or a pre-neoplastic change rather than a neoplasm. The hormonal levels in this case were within the normal range for estrogen and progesterone, and below limits for LH and FSH, for the female baboons in our colony. The significance of a one-time hormonal assay of an archived serum sample in this case is uncertain; however the reproductive data from this animal suggests a history of abnormal cycling.

There has been one other reported case of spontaneous true hermaphroditism (OT-DSD) in a rhesus macaque [9]. A 105 day-old rhesus macaque presented grossly as a female but histological examination of the gonads revealed bilateral ovotestes. Female sex chromatin was observed in motor neurons of the cervical spinal cord [9]. A previous case reported by Bielert et al, described the presence of gonadal dysgenesis (streak gonads) in a Chacma baboon (*Papio* spp) [14]. The case described by Bielert et al, shows significant differences from the present case, the Chacma baboon was a phenotypically eunuchoid female, which completely lacked the presence of sex skin, had a hypoplastic uterus, and menstrual bleeding was not observed. Histologically, both gonads were atrophied and consisted of adipose and fibrous tissue and lacked the presence of follicles or seminiferous tubules (streak gonads) [14]. Bielert et al reported a low level of testosterone and estrogen levels in the baboon, which is consistent with the gonadal dysgenesis. In contrast, the baboon in the present case was phenotypically a normal female, had recorded episodes of menstrual cycles, and apart from episodes of seizures (which are sporadic in colony baboons) [21], the animal had no major clinical history or signs suggestive of hermaphroditism. A case of pseudohermaphroditism in a baboon was reported by Wadsworth et al [22], in which the animal had external genitalia, gonads, and accessory sex glands, consistent with male phenotype, and the internal organs included a well-developed uterus and fallopian tubes [22].

Mammalian sexual development proceeds in three consecutive steps. First chromosomal sex is established, next gonadal sex is determined, and last phenotypic sex is developed. In humans, chromosomal sex determination occurs at fertilization resulting in a zygote that is either 46 XX or 46 XY. Initially, XX and XY embryos will have similar undifferentiated gonads, both mesonephric (Wolffian) and paramesonephric (Müllerian) ducts, and undeveloped external genitalia. Genetic sex will then normally determine gonadal differentiation. The Y chromosome contains the SRY gene (sex determining region Y), which is responsible for initiation of male development and is necessary for testes formation [4, 23]. Testicular tissue secretes two hormones: 1) MIH (Mullerian Inhibitory Hormone), which is responsible for the regression of Mullerian duct, and 2) testosterone, which will aid

in the development of male internal and external genitalia. In the absence of a Y chromosome, ovarian tissue forms. Although baboons have 42 chromosomes, sex determination is similar to humans [24]. Fluorescent in-situ hybridization for the SRY gene was attempted on frozen samples of skeletal muscle, kidney, and liver; however, it was unsuccessful after multiple attempts. No additional chromosomal or genetic testing was performed in this case.

Sex developmental disorders can occur either from chromosomal or genetic abnormalities or from inappropriate hormonal exposure during reproductive tract differentiation. In particular, formation of ovotestes can occur either from sex chromosome abnormalities (chimeric type 46 XX/46 XY or mosaic type) or from an abnormality during gonadal development resulting in sex reversal. In humans, most OT-DSD cases exhibit a 46, XX karyotype, followed by either 46, XX/46, XY chimeric type or mosaic type, with 46,XY being the least commonly observed [2, 25–27]. In cases of OT-DSD with a 46, XX karyotype, XX sex reversal can occur due to a translocation of the Y chromosome portion that contains the SRY gene, the main male sex-determining gene, to another chromosome, usually the X chromosome. Interestingly, SRY is only found in about 10% of 46, XX OT-DSD. This indicates that there may be an X-linked or autonomous sex-determining loci responsible for the presence of testicular tissue [25]. OT-DSD is rare in humans, accounting for 3 to 10% of all DSD cases [25].

We report the first case of OT-DSD (true hermaphroditism) in a baboon (*Papio* spp) and present a brief review of non-human primate literature. Due to the economic significance of breeding in livestock and farm animals, and with the recent advances in molecular cytogenetics, disorders of sexual development (and chromosomal abnormalities) have been extensively studied and widely reported in domestic animals. In contrast, they have rarely been reported in the non-human primate literature. So far, there has been only one reported case of true hermaphroditism in a rhesus macaque. It is logical to assume that actual number of cases in the non-human primates would be higher, but most cases are actually in wild conditions, or remain undiagnosed due to lack of histopathological assessment. The present case highlights the importance of examining the full reproductive tract both grossly and histopathologically in routine diagnostic necropsy cases.

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Figure 1(A–D). Ovotestes from a 19-year-old baboon (*Papio* spp.) with OT-DSD

A) Ovotestes showing both ovarian follicles (asterisk) and seminiferous tubules (arrows) (H&E). B and C) Follicles in various stages of maturation surrounded by ovarian stroma (H&E) D.) Seminiferous tubules lined by Sertoli cells with loss of germinal epithelium and lack of spermatozoa (H&E).

Figure 2(A–E). Uterus from 19-year-old baboon (*Papio* spp.) with OT-DSD

A) Uterus showing cystic endometrial hyperplasia and adenomyosis with endometrial glands extending deep into the myometrium. E = Endometrium; M = Myometrium (H&E). B) Endocervix showing cystic hyperplasia of endocervical glands and atypical proliferation of cervical mucosa. Black box highlights area of tissue shown in images D and E (H&E). C) Endocervical glands show abrupt transition from simple columnar epithelium to stratified non-keratinizing squamous epithelium (H&E). D) Epithelial cells within areas of squamous metaplasia exhibit nuclear immunoreactivity for the proliferation marker Ki-67 (DAB). E) Epithelial cells within areas of squamous metaplasia are negative for p16, a common marker used to identify cervical malignancies in humans (DAB).

Table 1

Serum hormone levels from OT-DSD baboon.

		Reference range (Female)	Reference range (Female)
Hormone	Present case	Unpublished colony data	Unpublished colony data (non-pregnant, luteal phase)
Estrogen (E2)	33.29 pg/mL	22.6 ± 95.59 pg/mL	363.94 ± 17.42 pg/mL
Progesterone (P4)	6.26 ng/mL	5.75–48.64 ng/mL	4.7 ± 1.78 ng/mL
AMH	19.31 ng/mL	Not Available	Not Available
Inhibin B	53 pg/mL	Not Available	Not Available
LH	0.0022 IU/ml	0.1 – 15.4 IU/mL	Not Available
FSH	0.002 IU/ml	0.8 – 21.1 IU/mL	Not Available
Testosterone	<0.025 ng/mL	0.47 – 1.78 pg/mL	Not Available

AMH = Anti-Müllerian hormone; LH = Luteinizing hormone; FSH = Follicle-stimulating hormone