Published in final edited form as:

J Am Anim Hosp Assoc. 2012 ; 48(2): 118–124. doi:10.5326/JAAHA-MS-5696.

Testicular Neoplasia in the Retained Testicles of an Intersex Male Dog

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Abstract

This case describes the presentation and management of an 8 yr old phenotypically female intersex male dog presented for evaluation of a mass in the right inguinal region. The right inguinal space was surgically explored, and a large irregular mass resembling a fully developed testicle was identified in the right vaginal tunic. A second mass resembling an atrophied, but anatomically mature testicle, was identified in the left tunic. The larger mass was identified as a Sertoli cell tumor that had replaced all normal testicular tissue. The smaller mass was identified as a testicle that contained a small intratubular seminoma. The patient was diagnosed as having a phenotypic female sex, chromosomal male sex, and a gonadal male sex. Hormone assays completed before and after the gonadectomy and mass removal document an elevation of circulating progesterone presurgically that returned to baseline by 1 mo postsurgically. The source of the progesterone was identified to be the Leydig cells of the atrophied testicle.

Introduction

The term “intersex” is used to describe a wide constellation of developmental reproductive abnormalities in which there is ambiguity between the phenotypic sex (i.e., external genitalia, location of the urethral opening, or presence of uterine tissue), genotypic sex (i.e., XX, XY, or some other variation), and gonadal sex (i.e., presence of ovaries, testes, or ovotestes). Pseudohermaphroditism occurs when there is gonadal tissue of one sex, but a genotypic or phenotypic sex that is inconsistent with the sex of the gonad. True hermaphroditism, on the other hand, occurs when an individual has both testicular and ovarian tissues present in the form of ovaries, testes, or ovotestes.

Histopathology, karyotyping, and proper identification of genitourinary anatomic makeup are all required to identify the presence of, and properly characterize, an intersex condition. The purpose of this report is to describe a case of a genetically male dog (78,XY) with a phenotypic female sex and a gonadal male sex.

Case Report

This report describes the case of an intact 8 yr old Labrador retriever that presented for a swelling in the right inguinal region. The owner reported no changes in the patient’s energy

level, skin or hair coat, weight, appetite, eliminations, or in the appearance of her vulva or mammary tissues. The owner first identified the mass 2 wk prior to presentation.

The dog was believed to be female due to the phenotypic appearance of her external genitalia (Figure 1). The owner reported that the patient was presented for ovariectomy at approximately 6 mo of age and that no internal reproductive organs were identified on exploratory laparotomy. To the owner's recollection, the patient had never displayed signs of an estrus cycle. No additional diagnostics were completed outside of the exploratory laparotomy at 6 mo of age according to the owner.

Physical examination findings included a mildly obese patient (body condition score was 4/5) who was bright, responsive, and active. The hair coat was in good condition. The abdomen was unremarkable on palpation. Cardiovascular and pulmonary systems were both normal. There was a 9 cm × 6 cm ovoid mass that was freely movable in the right inguinal space. The mass was nonpainful and did not appear to be attached to the subcutaneous tissues. There was a palpable band of tissue that extended from the mass upward into the inguinal space. There was mild nipple enlargement involving all mammary glands, but no mammary glandular enlargement was identified. There were paired dilatations of the skin along the proximal vulva that resembled a vestigial scrotum. The vulva appeared slightly elongated and the only opening was a 1 cm in diameter round opening at the terminus of the vulva (Figure 1 and Figure 2). Her physical examination was otherwise unremarkable.

Based on the physical findings of ambiguous genitalia and the history of no internal reproductive organs found during the laparotomy when the patient was 6 mo old, a tentative diagnosis of an intersex condition was made. There was a strong suspicion that the inguinal mass was gonadal in origin.

The owner elected to proceed with surgical exploration of the mass, but declined preoperative imaging such as ultrasonography to help identify the structure of the mass. Preanesthetic chemistry and complete blood cell counts were all within the reference ranges. Two-view plain film radiographs of both the abdomen and chest were unremarkable.

The patient was premedicated with butorphanol^a (2 mg/kg) and dexmedetomidine^b (2.0 µg/kg) intramuscularly. Anesthesia was induced using 5 mg/kg propofol^c given IV to effect. A surgical plane of anesthesia was maintained using isoflurane^d inhalant anesthesia.

At surgery, the mass identified on physical examination was located and found to be encapsulated within the vaginal tunic. The mass appeared to have a mature epididymis, vas deferens, and a pampiniform plexus (Figure 3 and Figure 4). The mass was removed using an open castration technique by first ligating the vascular bundle along with the vas deferens using a pair of simple encircling ligatures. The tunic was closed with a simple encircling suture and returned to the inguinal space. The skin was closed routinely. Given a high index of suspicion for bilateral cryptorchidism, an exploratory incision was made over the left inguinal space and the vaginal tunic was exposed via blunt dissection. A small testicle was identified within the tunic (Figure 4). This gonad was removed using a technique identical to the contralateral side. Recovery was routine. The patient was discharged from the hospital and prescribed carprofen^e 2 mg/kg *per os* q 12 hr for 5 days for pain management.

^aTorbugesic; Fort Dodge Animal Health, Overland Park, KS

^bDexDomitor; Pfizer Animal Health, Kalamazoo, MI

^cPropofol; Abbott Animal Health, Abbott Park, IL

^dIsothesia; Butler Animal Health Supply, Dublin, OH

^eNovox; VEDCO, St. Joseph, MO

Several sections of the large mass, including the peripheral mass adjacent to the epididymis, were submitted along with the entire smaller gonad for histopathology to the IDEXX Laboratory in Portland, MA. The larger mass in the right tunic was comprised of cells with moderate cytoplasm, open-faced oval nuclei, and occasional mitotic activity. Cells formed palisading arrays. There were no Leydig cells identified in the biopsy sample. The diagnosis of Sertoli cell tumor extending to sample margins with no normal gonadal tissue was made. The smaller mass consisted of normal, atrophied, testicular tissues that had been partially replaced by intratubular infiltrates of neoplastic cells. The neoplastic cells formed sheets, aggregates, and clusters of discrete round cells that exhibited scant to moderate cytoplasm, rounded to angular hyperchromatic nuclei, and multiple prominent nucleoli. The tissue was therefore identified as an anatomically complete, but atrophied, testicle with mild infiltration of an intratubular seminoma.

The serum that had been collected at the time of surgery was frozen at -20°C . A second sample was collected 5 wk after the first, and these paired samples were submitted for estradiol, testosterone, and progesterone levels. The estradiol and testosterone levels were low both before and after surgery, but the progesterone serum concentrations decreased from an active production range to baseline after surgery (Table 1).

Heparinized blood was collected from the patient for cytogenetic evaluation of short-term peripheral lymphocyte cultures as previously described.¹ Fifty nonbanded metaphase spreads were evaluated and all revealed both an X and a Y chromosome constituting a 78,XY karyotype (Figure 5). Polymerase chain reaction was positive for the presence of the sex-determining region on the Y chromosome, the *SRY* gene (Figure 6).²

Immunohistochemistry for progesterone was used to identify the source of progesterone. Rehydrated formalin-fixed paraffin-embedded sections of tumor and testicle were incubated with a polyclonal antibody against progesterone^f. An appropriate biotinylated secondary antibody was used, and the signal was detected using a peroxidebased chromogen^g. There was no positive staining associate with any cells within the Sertoli cell tumor (Figure 7). Positive staining was identified in the Leydig cells within the atrophied testicle (Figure 8).

Based on these findings, the patient was diagnosed as a 78,XY male pseudohermaphrodite. Surgical excision of both tumors appeared to be complete. The patient has continued to do well postoperatively with no adverse events related to the procedure.

Discussion

There have been no studies evaluating the precise incidence of intersex conditions in the overall canine population. The reported cases of intersex in the literature span a wide variety of morphologies with a large number of breeds represented.³ There are several breeds, however, with proven inherited intersex conditions. For example, XX sex reversal is a heritable condition in the American cocker spaniel. Defects in androgen-dependent masculinization are believed to be familial in the Boston terrier.⁴ Persistent müllerian duct syndrome (PMDS) is reported as the most common form of intersex in the canine.³ PMDS is known to have a familial association in schnauzers, but been described in many different breeds including the Labrador retriever, basset hound, cocker spaniel, and standard poodle.^{3,5} Despite the identified breed predilections to different disorders of sex development in the dog, the overall incidence of intersex in the canine population remains rare.

^fTVMDL Rabbit P4 Antibody; Texas Veterinary Medical Diagnostic Laboratory, College Station, TX

^gNovaRED; Vector Laboratories, Inc., Burlingame, CA

By comparison, the incidence of intersex in humans is approximately 0.018%, depending upon the specific definition of intersex used.⁶ In addition, an Australian study evaluating the incidence of intersex conditions of pigs presented to the abattoir for slaughter found the total incidence of intersex to be approximately 0.4475%.⁷ Among polled goats of the Saanen, Toggenburg, and Alpine breeds, intersex is considered a common condition, reported in between 2% and 11% of individuals.⁸

The phenotype of the intersex condition can vary from a nearly “normal” individual with decreased fertility to an individual with any combination of male and/or female external and internal reproductive organs.⁴ It is the ambiguous sex phenotype that usually prompts the investigation of the presence of an intersex condition. Other potential historical clues as to the presence of an intersex condition include hypospadias, clitoral enlargement, the presence of an os clitoris, or persistent anestrus or infertility.⁹

If the patient is scheduled for spay or neuter, the presence (or absence) of internal reproductive organs and their histologic identification can further characterize the type of intersex. A phenotypically female dog with male gonads is referred to as a male pseudohermaphrodite. Similarly, a phenotypically male dog with ovaries is considered a female pseudohermaphrodite. Female pseudohermaphroditism is considered very rare compared with male pseudohermaphroditism.⁹

The chromosomal genetic makeup of intersex individuals varies. Dogs with a normal karyotype have 78 chromosomes including the sex chromosomes. Genetic sex is determined at the time of fertilization and fusion of the haploid gametes into the diploid embryo. Normal genetic sex is either XX (female) or XY (male). Intersex individuals may also have 79,XXY, 77,XO (i.e., the absence of a second X chromosome), or in the case of true chimerism, the karyotype is 78,XX/XY. The *SRY* gene is located on the Y chromosome and is important for initiation of male embryonic gonadal development. Deletion or dysfunction of the *SRY* gene therefore equates to a phenotype of female even if the genotype includes the Y chromosome.^{4,10}

Differentiation of the male phenotype in the 78,XY individual involves a complex series of events in which testosterone promotes differentiation of the Wolffian ducts into the epididymis and vas deferens. Sertoli cells within the testicle secrete Müllerian inhibiting substance, which triggers regression of the Müllerian ducts (i.e., the female tubular tract). Testosterone is converted to dihydrotestosterone (DHT) by 5 α -reductase expressed in the tissues of the urogenital sinus, genital tubercle, and genital swellings. The presence of DHT induces these tissues to differentiate into the urethra, prostate, penis, and scrotum. Failure to produce 5 α -reductase, failure of enzyme function, or resistant or nonfunctional androgen receptors can cause varying degrees of feminization of the genitalia in a genetically male dog. Insensitivity of tissues to the androgen hormone DHT is referred to as androgen insensitivity syndrome. Failure to produce 5 α -reductase has not been described in dogs, but is an inherited autosomal recessive trait in humans.⁴ A case of nonfunctional DHT receptors with subsequent feminization of the genitalia has been described in the canine.¹¹

The patient in this case study has characteristics consistent with a failure of androgen-mediated phenotypic sex differentiation. It was not possible to fully characterize the presence or absence of internal genitalia that would be required to definitively prove a diagnosis of PMDS versus a failure of androgen-dependent masculinization. The owner declined MRI and an ultrasound of the abdomen due to cost. If the owner's reported findings of the laparotomy performed when the patient was 6 mo old are accurate, it is reasonable to assume that there was no uterus or Müllerian ducts. It was not possible to determine the function of DHT receptors in this patient, as this requires fibroblast cell cultures, which was

not technically feasible. Therefore, given the information available, it is most likely that this patient has dysfunction of the DHT receptors required for masculinization.

Treatment of the intersex condition depends entirely upon what abnormalities or symptoms are present. Therapeutic goals include establishment of a functional urinary tract (as in hypospadias), removal of gonads to prevent reproduction and prevent development of disease associated with retained or abnormal gonads, and reconstruction of the external genitalia (if necessary) for normal function. Many intersex animals will not require treatment of their anatomic abnormalities, but gonadectomy is strongly recommended in all affected individuals.⁹ Neoplasia associated with the gonads of intersex individuals has been described.^{12–14} There are no studies specifically addressing the incidence of neoplasia of the reproductive tract in intersex animals compared with the general population. In cases of ambiguous or incompletely developed genitalia, it is feasible that conditions predisposing an individual to develop neoplasia of the reproductive organs may be missed. The patient described in this case study is an excellent example of this concept. Cryptorchidism was not diagnosed at a young age, and this condition predisposed this patient to develop neoplasia in the retained testicle.

There is a significantly increased risk of neoplasia in the retained versus the normally descended testis. The relative risk factors published are 14.3, 13.6, and 9.2.^{15–17} The data are mixed regarding the most common tumor type encountered. There is similar contradiction regarding the prevalence of tumor types in the retained versus the descended testicle. One study indicates that Sertoli, seminoma, and interstitial cell tumors all occur with relatively equal frequency in both retained and descended testes.¹⁸ Another study published in 2009 out of Taiwan reported that Sertoli cell and mixed germ cell-sex cord stromal cell tumors accounted for >67% of tumors within retained testes.¹⁹ Of all testicular tumors, that same study reported that mixed germ cell-sex cord stromal cell tumors and Sertoli cell tumors are more likely to occur (2.6 times and 2.2 times, respectively) in retained testes, seminomas are equally distributed between retained and scrotal testes, and interstitial cell tumors are 3 times more likely to be found in the scrotal testicle. Overall frequency of tumor types in feral dogs in Mexico and client-owned dogs in Italy were found to be similar to those identified in Taiwan.^{15,20} However, neither of those studies reported data regarding incidence of tumor types in relation to retained versus descended testes. These reports are in stark contradiction to an earlier study of dogs in the United States that reported Sertoli cell tumors to be the more common tumor of retained testes.¹⁶ The American study also reported a roughly equal incidence of Sertoli cell tumors and seminomas in the retained testicles whereas interstitial cell tumors were nearly exclusively identified in the scrotal testes.

The changes in the hormone profile completed after gonadectomy confirm the presence of elevated progesterone at the time of surgery. The source of progesterone production in this patient was shown to be the Leydig cells. Under normal circumstances, the Leydig cells, under regulation by luteinizing hormone, would be responsible for the production of testosterone from cholesterol. Progesterone is an early intermediate in this pathway. In humans, it has been shown that very small amounts of progesterone are produced by the Leydig cells.²¹ Under typical conditions of cryptorchidism the retained testis should continue to produce testosterone, albeit in lower amounts.²² Measurable amounts of progesterone would not be expected to be found in the peripheral blood under normal circumstances.

Hyperprogesteronism associated with Sertoli cell tumors has been described in the literature for two dogs.^{23,24} In one case, only hyperprogesteronism was identified and clinical signs were limited to alopecia. In the second case, hyperestrogenism and hyperprogesteronism

were identified. Clinical signs in that patient included hematuria, prostatitis, and prostatomegaly, which was presumed to be endocrine-induced. In both cases, clinical signs resolved after castration and removal of the Sertoli cell tumor. The variability in those two cases was likely due to compounding factors such as concurrent hyperestrogenism, duration of hyperprogesteronemia, and the variability in serum progesterone values between the cases.

In this case described in this report, the increased serum progesterone could be explained by impaired function of the enzyme 17-hydroxylase in the Leydig cells. Dysfunction of this enzyme would affect progesterone conversion to 17-hydroxyprogesterone, which could potentially lead to an increase in progesterone and a deficiency of testosterone. The patient described in this case clearly had some functional 17-hydroxylase as this dog did not have an absolute deficiency of testosterone. Testosterone is required for the development of the vas deferens and epididymis, both of which were identified at the time of surgery. It is unknown if any secretory products of the Sertoli cell tumor could be indirectly responsible for the increase in progesterone, but it is considered unlikely. The progesterone levels measured in this patient were not associated with overt clinical signs and could have been present for much of the patient's adult life. It is interesting to consider, however, that this is the third case reported in the literature of hyperprogesteronemia associated with the presence of a Sertoli cell tumor; therefore, a causal relationship between the two cannot be ruled out.

Progesterone excess is an uncommon problem in the canine patient. Excess of progesterone in male dogs is typically associated with hyperadrenal disease (i.e., over function of the zona reticularis either due to a primary adrenal tumor or secondary to pituitary stimulation). Symptoms of hyperprogesteronism are typically limited to alopecia, especially on the flank and dorsum (i.e., an "endocrine" alopecia).²⁵ Severe excess of progesterone can result in acromegaly, which is usually associated with exogenous administration of high doses of progesterone, but can occur during the diestrus phase of the estrus cycle in the aged intact female dog. Clinical signs of acromegaly typically include diabetes mellitus, respiratory stridor, cardiomyopathy, and myxedema of the tissues around the head and neck.²⁶ The patient in this case study did not have any symptoms consistent with acromegaly and did not have any areas of alopecia. This may be due to the relatively modest increase in progesterone levels measured in this patient.

Primary testicular tumors are metastatic in <15% of cases. Sertoli cell tumors and seminomas are the most likely tumors to demonstrate a metastatic phenotype. Metastasis is typically seen first in regional lymph nodes and, ultimately, to distant sites such as the lung.¹⁸ Since the regional nodes draining the tunic are sublumbar and intra-abdominal, imaging (such as ultrasound, computed tomography, and plain film radiography) would be useful to identify potential metastasis. In addition, given the presence of hyperprogesteronemia on presentation, repeat progesterone levels may be useful to help identify the presence of recurring disease in this case.

Conclusion

The patient described in this report was genetically male (78,XY) with a female phenotype and male gonads. The patient was diagnosed with bilateral cryptorchidism, a Sertoli cell tumor, an intertubular seminoma, and hyperprogesteronism. The hyperprogesteronemia resolved within 5 wk postcastration. The source of the increased progesterone was determined to be the testicular Leydig cells.

Intersex conditions occur infrequently in dogs. It is important that reasonable attempts be made to locate the gonads of individuals suspected of intersex condition so a proper diagnosis of the intersex state can be made. Once diagnosed, appropriate treatments, if any,

can be considered. Proper diagnosis of this patient as a young dog at the time of surgery would have eliminated the potential for gonadal neoplasia.

In this case, it is hoped that surgical intervention and removal of both the seminoma and Sertoli cell tumor will provide an excellent long-term prognosis, although regular monitoring for metastatic disease is required.

Acknowledgments

This study was supported in part by the National Institutes of Health Grant #RR02512.

Glossary

DHT	<i>dihydrotestosterone</i>
PMDS	<i>persistent müllerian duct syndrome</i>

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FIGURE 1.
Photograph of the external genitalia. The hair has been shaved in preparation for surgery.

FIGURE 2.
A closer image of the vulva/hypoplastic prepuce.

FIGURE 3.
Surgical appearance of the Sertoli cell tumor.

FIGURE 4.
Photograph of both the Sertoli cell tumor (*right*) and the atrophied testicle (*left*).

FIGURE 5.
Karyotype of the patient described in this report. The X and Y chromosomes are labeled.

FIGURE 6.

SRY PCR. Lane 1: PhiX 174 size marker. Lane 2: Normal male control showing SRY specific band at approximately 118 bp and the expression control marker (*Glast*) at approximately 194 bp. Lane 3: Normal female showing only the expression control marker. Lane 4: Amplicon from the patient's sample showing both the SRY and the expression control bands. The *Glast* gene is not associated with any sexual phenotype but is used as a control to ensure amplification.

FIGURE 7.

Representative image of the immunohistochemistry for progesterone in the Sertoli cell tumor. No positive staining is found within any cells. NovaRed chromagen. No counter stain. Magnification $\times 40$.

FIGURE 8.

Representative image of the immunohistochemistry for progesterone in the left testicle. Positive staining is noted within the cytoplasm of the Leydig cell (*black arrow*). NovaRed chromagen. No counter stain. Magnification $\times 40$.

TABLE 1

Sex Steroid Hormone Values Pre- and Postsurgically

Test	Presurgically	5 wk postsurgically	Reference range for an adult intact male
17 β -estradiol	0.0 pg/mL	0.0 pg/mL	0.0–20 pg/mL
Testosterone	<200 pg/mL	<200 pg/mL	200–10,000 pg/mL
Progesterone	2.0 ng/mL	<0.20 ng/mL	<0.2 ng/mL