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Case Report

Canine Sertoli cell tumor: anti-Müllerian hormone, inhibin B, and estrone sulphate

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Abstract

A unilaterally castrated male boxer was referred for chronic generalized alopecia and pruritus. Physical examination revealed symmetrical alopecia, pendulous prepuce, lichenification of the scrotum, and enlargement of mammary papillae. Penile/preputial cytology revealed superficial epithelial cells. Transabdominal ultrasonographic examination revealed a globoid mass with heterogenous echogenicity in the left caudal abdomen. The presumptive diagnosis was Sertoli cell tumor (SCT) associated with cryptorchidism. Exploratory laparotomy and histology of the removed mass confirmed the diagnosis. Three weeks after surgery, serum anti-Müllerian hormone (AMH) concentrations decreased from 8,435 to 56 ng/ml and inhibin B decreased from 805 to < 6 pg/ml. Two months after surgery dermatoses subsided and there was substantial regression of enlarged nipples. This report highlights the diagnostic value of practical procedures (penile/preputial cytology, transabdominal ultrasonography, and measurement of serum AMH and inhibin B concentrations) to aid in the diagnosis of cryptorchidism and SCT, especially in patients with generalized skin conditions.

Keywords: Cryptorchidism, feminization, paraneoplastic syndrome

Background

Canine Sertoli cell tumor (SCT) is the most common testicular neoplasm associated with feminization syndromes. The prevalence of feminization in cases of SCT has been reported as 24[1] and 39%,[2] with an increased frequency of the syndrome occurring in cryptorchid testes.[2] Clinical signs of feminization are consequent to hyperestrogenism associated with a secretory tumor. These include bilateral symmetrical alopecia of the trunk and flanks, hyperpigmentation of inguinal skin, gynecomastia, pendulous prepuce, squamous metaplasia of the prostate, and attraction by male dogs. Preputial cytology is a useful diagnostic aid in cases of SCT to determine the effects of estrogens on preputial epithelial cells; a bioassay for hyperestrogenism particularly, for dogs with feminizing signs. Additional methods of diagnosis include imaging, exploratory surgery, and histology. Limited studies have evaluated the endocrine characteristics of canine SCT. Serum estradiol concentrations had variable elevation,[3–6] whereas inhibin concentrations increased in SCT dogs compared to controls.[3,5] Serum anti-Müllerian hormone (AMH) concentrations were determined in patients with testicular and other tumors.[6] These findings suggested that canine SCTs secrete several hormones that have diagnostic potential. This report describes a case of canine SCT with feminization syndrome and evaluation of serum AMH, inhibin B, and estrone sulphate concentrations before and after tumor removal.

Case presentation

A 6-year unilaterally castrated (at 6 months of age) male boxer was presented with a history of chronic alopecia and pruritus. Approximately 18 months after castration, the patient developed dermatoses and was treated for presumed atopic dermatitis for several years until referral.

At presentation, the patient's dermatologic lesions included diffuse alopecia, moderate to severe lichenification and scaling along the sternum, axillary region, and on medial thighs (bilateral). The scrotal skin had lichenification and edema, and the prepuce was moderately pendulous and edematous. Mammary papillae were enlarged, elongated, and mildly edematous (Figures 1 and 2). The owner reported that changes to the prepuce and mammary papillae had developed concurrent with signs of alopecia. The patient was receiving 6

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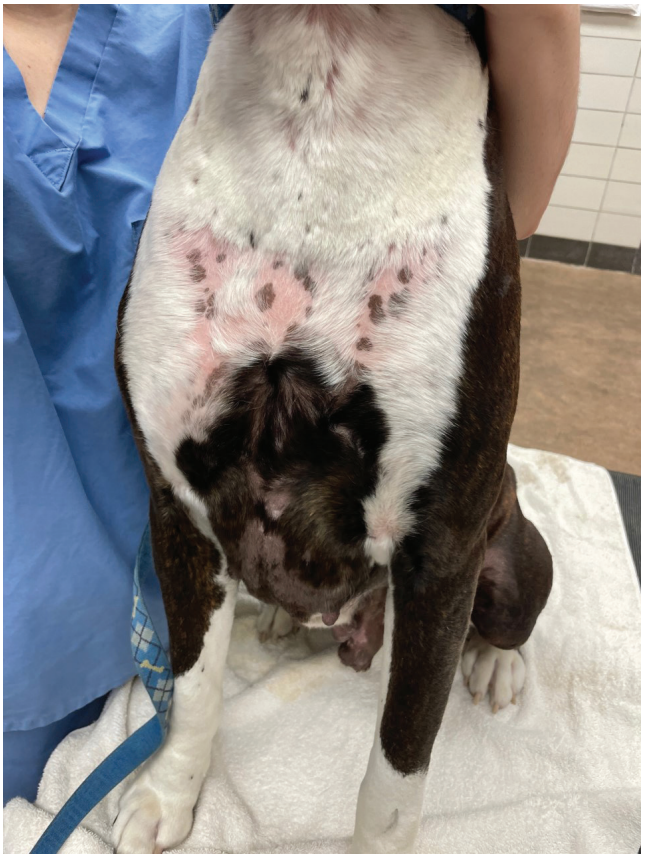

Figure 1. Sternum, mammary gland, and prepuce (note diffuse alopecia across sternum, enlargement of mammary papillae, and pendulous prepuce)

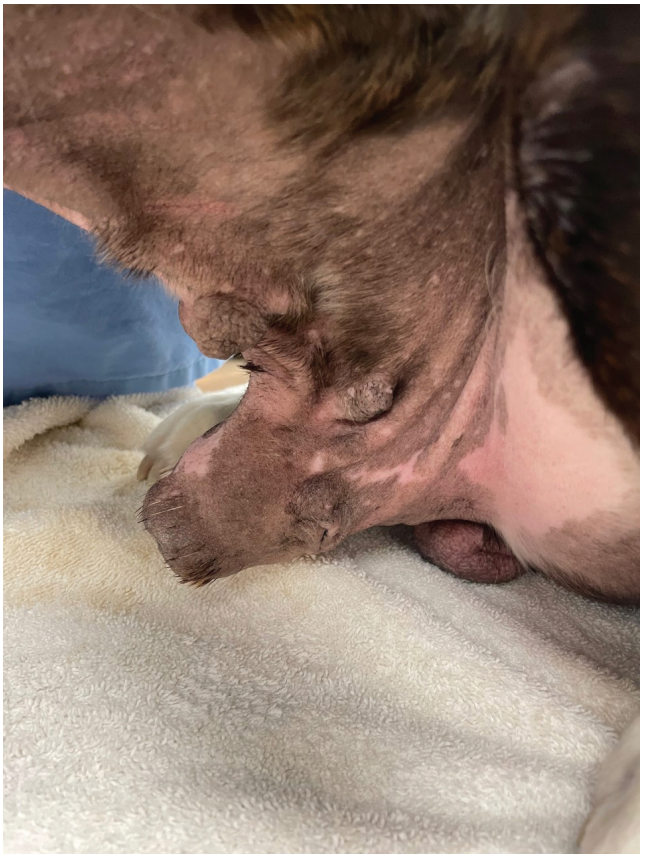

Figure 2. Mammary gland and prepuce (note diffuse ventral alopecia, enlarged mammary papillae, and pendulous prepuce)

monthly injections of lokivetmab (a monoclonal antibody that acts against interleukin 31) for suspected atopic dermatitis. Preputial cytology revealed superficial epithelial cells.

Transabdominal ultrasonography revealed an oval to globoid mass (4.2 × 3.3 cm) with irregular contour (suspected left testis), located ventro-cranially and slightly left to the urinary bladder. The mass appeared moderately cystic and heterogenous in echogenicity, with no distinct mediastinum testis (Figure 3). Mild to moderate iliac lymphadenopathy and splenic nodules were observed. Prostate measurements (35 × 32 × 40 mm) were within normal parameters for an intact dog of the patient's size and age.[7,8]

Fine needle aspirates of the left medal iliac lymph node and spleen were consistent with reactive lymphoid hyperplasia and splenic nodular hyperplasia with low-grade extramedullary hematopoiesis, respectively. Thoracic radiographs had no evidence of pulmonary metastases. Complete blood cell count and serum biochemistry revealed no abnormal findings.

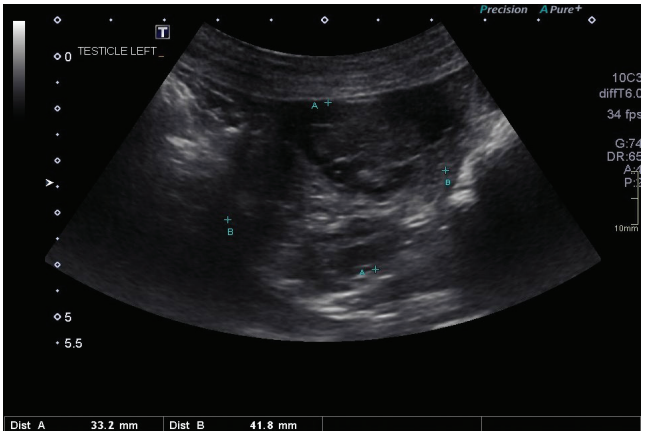

Figure 3. Oblique ultrasonographic image of the irregular mass (33.2 mm between calipers A and 41.8 mm between calipers B) of suspected retained left testis (note moderate cystic and heterogenous echogenicity appearance)

Treatment

An exploratory laparotomy was performed. The suspected retained left testis was lateral and adjacent to the left aspect of the urinary bladder. The left testis and a section of the spermatic cord with which it was associated, and the enlarged left medial iliac lymph node were surgically removed. Tissues were submitted for histological evaluation.

Pathology

The left testis had a multinodular appearance and measured 5.0 × 4.0 × 3.5 cm (Figure 4). The cut surface had a tan, soft,

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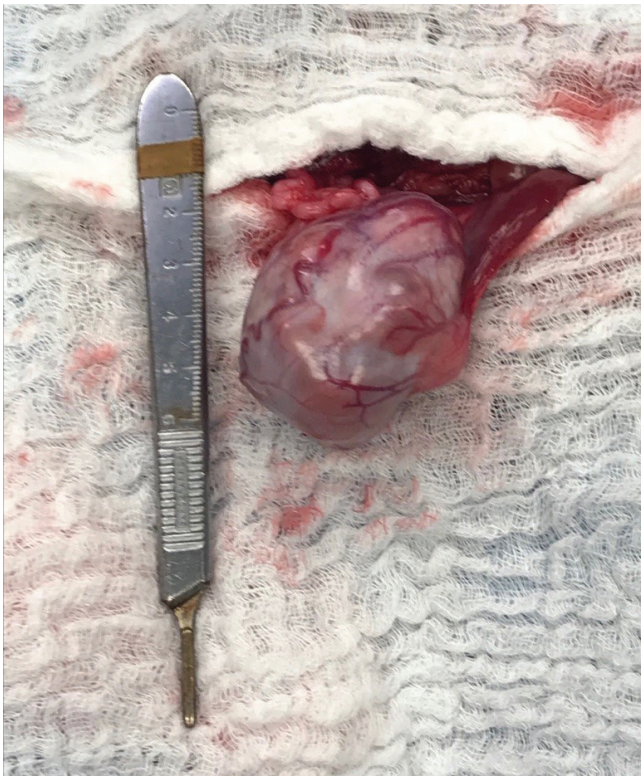

Figure 4. Photograph of retained left testis (note multinodular appearance and irregular contour) and pampiniform plexus to its right

multinodular mass with multiple cysts containing brown fluid. Microscopic examination of the abdominal mass confirmed its testicular origin. Structures identified included seminiferous tubules, epididymis, and pampiniform plexus. The testis appeared enlarged and partially replaced by a neoplastic mass consistent with a SCT of diffuse growth pattern (Figure 5a). The neoplasm was partially encapsulated, infiltrative, multilobulated, composed of polygonal to elongated cells (Figure 5b) forming variably sized, coalescing lobules separated by a moderate amount of fibrous stroma and palisading along the connective tissue trabeculae. Neoplastic cells had distinct cell borders, eosinophilic to amphophilic, finely granular or clear vacuolated cytoplasm, and round to oval nuclei with finely stippled chromatin and a variably distinct nucleolus. Mild anisocytosis and anisokaryosis were present, with a mitotic count of 15 per 2.37 mm^2 (equivalent to 10 FN22/400X fields or 10 high-power fields) (Figure 5d). Frequent neoplastic cells within blood vessels (tumor emboli) were also noted, including a small cluster of neoplastic cells in the pampiniform plexus (Figure 5c). Seminiferous tubules that remained at the periphery of the neoplasm were small and devoid of germ cells, denoting marked atrophy (Figure 5d) and the epididymis was similarly observed that was devoid of sperm. No evidence of metastasis was detected in the left medial iliac lymph node.

Endocrinology

Serum samples were sent to UC Davis Endocrinology Laboratory for AMH, inhibin B, and estrone sulphate analysis by Enzyme-Linked Immunosorbent Assay (ELISA). Serum was collected prior to and 3 weeks after surgery. Serum AMH concentrations decreased from 8,435 to 56 ng/ml after tumor removal (reference interval reported as < 0.15 ng/ml for castrated dogs; Ansh Labs, Webster Texas). Serum inhibin B concentrations similarly decreased from 807 to < 6 pg/ml. Estrone sulphate concentrations were 1.5 ng/ml before surgery and 1.3 ng/ml after surgery (reference ranges for estrone sulphate and inhibin B were not reported by the laboratory).

Outcome

Dermatoses resolved 6–8 weeks after surgery. The enlargement of the mammary papillae was largely resolved by 6 months after surgery. Cranial thoracic mammary papillae were still mildly enlarged; however, the remaining papillae had returned to normal size. The patient's signs of pruritus were satisfactorily controlled with biannual injections of lokivetmab. Consultation with the oncology service for tumor surveillance was recommended 3 months after tumor removal but was declined by the owner.

Discussion

The patient was presented with a history of chronic alopecia that poorly responded to long-term treatment for allergic dermatitis. An estrogen-secreting SCT was the cause of the patient's hair loss. Hyperestrogenism due to exogenous or endogenous sources of estrogen is a known cause of noninflammatory alopecia.[9] Clinical signs of alopecia associated with hyperestrogenism are derived from the binding of estrogen-to-estrogen receptor α that is involved in the regulation of hair follicle cycle. This binding alters the anagen-telogen phase transition of the hair follicle cycle by inducing premature catagen (regression stage) and prolonging telogen (resting phase).[10] This results in a failure of hair growth that can mimic inflammatory and other noninflammatory causes of alopecia. Additional signs of feminization, including elongation of the mammary papillae and pendulous prepuce during clinical examination, prompted assessment for potential exogenous or endogenous sources of estrogen. This highlighted the importance of a thorough and problem-based approach to the clinical investigation of alopecia in male dogs. The persistence of mild pruritus after resolution of alopecia suggested that an unrelated source of inflammatory dermatitis was possible.

Superficial epithelial cells comprised the dominant cell type identified on preputial cytology, consistent with hyperestrogenism. Preputial cytology has previously been demonstrated to be a useful investigative tool in cases of SCT, in which the presence of > 20% superficial epithelial cells, as a predictor of elevated serum estradiol concentrations, had a sensitivity and specificity of 80 and 90%, respectively.[11] In addition to preputial cytology, abdominal ultrasonography was an important diagnostic modality employed to determine the cause of feminization in the current patient. Abdominal ultrasonography permitted identification and localization of the retained testis, facilitating a rapid diagnosis and preparation for surgical removal.

Anti-Müllerian hormone

AMH is a glycoprotein hormone that belongs to the transforming growth factor (TGF) β-family.[12] Secretion of AMH from Sertoli cells is most pronounced during fetal

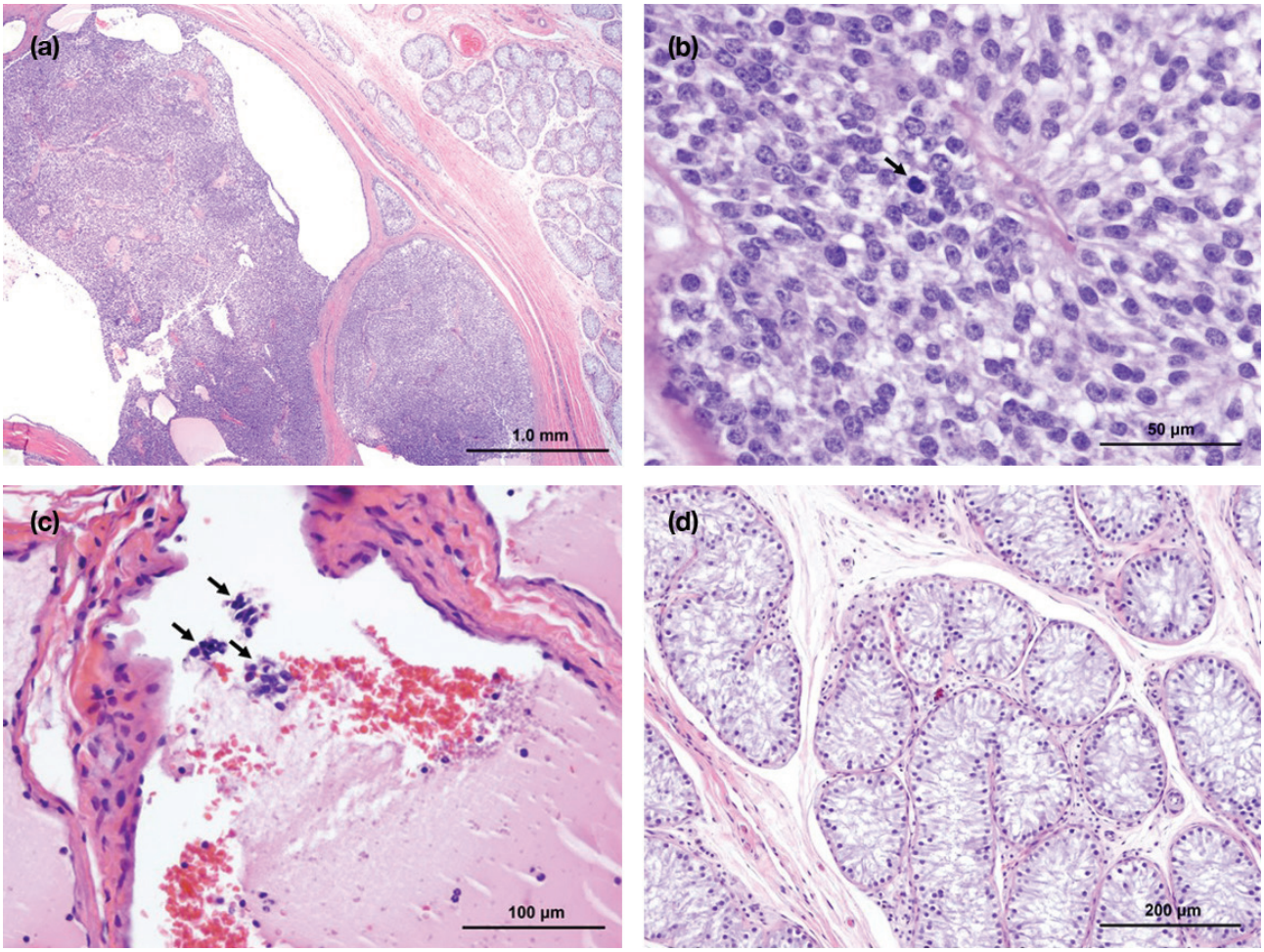

Figure 5. Representative photomicrographs of histology of cryptorchid left testis. (a) Sertoli cell tumor compressing the markedly atrophied testicular parenchyma; bar = 1 mm. (b) Polygonal to elongated neoplastic cells palisading along the connective tissue trabeculae. A mitotic figure is in the center (arrow); bar = 50 µm. (c) Small clusters of tumor emboli (arrows) present within a vein in the pampiniform plexus; bar = 100 µm. (d) Atrophic testicular parenchyma with Sertoli cells in shrunken seminiferous tubules devoid of germ cells; bar = 200 µm.

development and prior to puberty. In male fetus, AMH signals Mullerian duct regression, preventing formation of uterine tubes, uterus, and cranial vagina.[13] AMH may have a role in regulating Leydig cell proliferation, function, and testosterone production.[14] During fetal development and prior to puberty, follicle-stimulating hormone (FSH) promoted the production of AMH whereas gonadal testosterone had an inhibitory effect on AMH secretion after puberty onset.[15] However, the basal expression of AMH throughout life is independent of gonadotropins.[16]

AMH has been a useful predictor for the presence of testicular tissue in dogs,[17,18] horses[19] and calves[20] for scrotal and cryptorchid testes. Limited studies have also investigated its value as a clinical biomarker for canine SCT. Immunohistochemical analysis of 24 SCT expressed AMH.[21] In the same study, the Sertoli cells of unaffected fetuses and pups < 45 days also expressed AMH whereas the Sertoli cells of older pups and adult dogs did not. The contrast in AMH expression between normal adult and SCT testes may attest to the diagnostic potential of AMH in canine SCT. Serum AMH concentrations in dogs with SCTs were > 22 ng/ml compared to control dogs that returned to normal concentrations (< 10 ng/ml).[6] In this study, concentrations of serum AMH in CSCT patients were significantly elevated compared to dogs in both control and other tumor groups.

Serum AMH concentration declined precipitously after surgery. A similar trend was observed[22] where a patient that was investigated for nonpruritic alopecia had markedly elevated serum AMH concentrations compared to 2 intact control dogs. A SCT affected cryptorchid testis was identified, and 3 months following surgical removal, serum AMH concentrations declined in this patient to concentrations similar to 2 castrated control dogs.

Serum AMH concentrations after surgery were 56 ng/ml. Serum AMH concentrations reference ranges (Ansh Labs, Webster, Texas) for intact and castrated male dogs are 0.2–73.4 ng/ml and < 0.15 ng/ml, respectively. In this patient, AMH concentrations therefore did not decline to baseline concentrations 3 weeks after surgery. There are no reports on the half-life of AMH in dogs, although a relatively prolonged half-life of 1.5 days has been described in stallions.[19] Persistence of AMH above baseline concentrations 3 weeks after surgical removal of the SCT may reflect a similarly long half-life in

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dogs, the marked elevation in serum AMH prior to surgery, or the presence of a secondary tumor.

Inhibin B

Inhibin is a glycoprotein hormone that contains an α and 1 of 2 possible β subunits designated βA (inhibin A) or βB (inhibin B).[23] Inhibin B is the predominant isoform in the adult male of several species including boar,[24] stallion,[25] rat,[26] and human.[27] Inhibin exerts a regulatory role on FSH secretion from the anterior pituitary gland. Production of inhibin is stimulated by FSH, whereas inhibin has a conversely inhibitory effect on FSH release, completing a negative feedback loop.[28]

The principal source of inhibin has historically been considered to be Sertoli cells.[28] However, inhibin subunits were expressed in Leydig or germ cells and the cellular source of inhibin varied with species and changed during transitions from fetal, neonatal, and adult life.[29–33] Inhibin α expression was only detected in Sertoli cells of neonates,[34,35] whereas inhibin was expressed in Leydig cells of both neonate and adult testes.[35,36] These studies indicated a possible shift of inhibin production from Sertoli to Leydig cell origin from neonatal to adult life in dogs. Reports on inhibin expression in canine SCTs have been inconsistent. Inhibin α was expressed in 13 of 21 canine SCT[34] and none of the 5 canine SCTs.[36]

Serum inhibin B in this case markedly declined from 805 ng/ml prior to surgery to nondetectable concentrations (< 6 pg/ml) at 3 weeks after tumor removal. Concentrations of serum inhibin B have not been reported in dogs. Inhibin detected by radioimmunoassay (RIA) has been reported for normal intact and castrated dogs as 0.51–2.50, and 0.05–0.11 ng/ml, respectively.[37] Antibody utilized in this assay is known to detect many forms of inhibin, including the free α subunit and inhibin α-β dimers (inhibin A and B).[38] Therefore, it is not possible to make a direct comparison between inhibin B concentrations determined by ELISA in the present report inhibin concentrations were determined via RIA.

Given the rapid decline in inhibin B to noneditable concentrations after tumor removal, it would seem reasonable to suspect that the neoplastic testis to be the origin of this hormone in the patient prior to surgery. In the absence of reference ranges for normal intact males, it cannot be determined if concentrations of inhibin B in patient's presurgical serum sample were due to the presence of normal or neoplastic testicular tissue. The hypothesis that a SCT may be a source of peripheral elevations in serum inhibin concentrations is supported.[3,5] An increase in serum inhibin-like immunoreactivity was (determined by RIA) detected in 9[5] and 5[3] dogs with SCT compared to controls. Further studies to investigate the potential of inhibin B as a marker of gonadal status or neoplastic conditions of the testis may be warranted.

Estrone sulphate

Estrogen is produced in the male gonad by the aromatization of androgens through the action of cytochrome P450 aromatase.[39] In mammalian species testes, aromatase expression has been predominantly localized to Leydig cells. However, species variations in the cellular distribution of this expression across Leydig, Sertoli, germ cells, and sperm exist.[39] Cellular expression of aromatase has also been documented in canine SCTs.[40] Estrogens in circulation are comprised of 3 forms: estradiol, estrone, and estriol. Conjugation of estrone by estrone sulfotransferase resulted in the formation of estrone sulphate.[41] Estrone sulphate is produced in substantial quantities in stallion[42] and boar[43] testis and by the feto-placental unit of many domestic species including mare,[44] ewe,[45] doe,[46] and sow.[47]

Estradiol concentrations have been variably elevated in cases of SCT[3–6] and did not always correlate with feminization.[3] Dogs with SCT had significantly higher estradiol concentrations compared to controls, although estradiol was only above the reference range for some patients.[4,5] It has been suggested that clinical signs of feminization with normal estradiol reflect secretion of other forms of estrogen by SCTs.[4] In the present case, serum estrone sulphate concentrations were 1.5 and 1.3 ng/ml in pre and postsurgical samples, respectively. Minimal changes in serum estrone sulphate concentrations after tumor removal in this patient may reflect extra-gonadal sources. However, in the absence of established reference ranges for estrone sulphate in male castrated or intact dogs, the interpretation of this result is largely speculative. The clinical significance of this finding remains undetermined.

Histological examination of the neoplastic testis and spermatic cord revealed tumor emboli within testis and pampiniform plexus blood vessels, implicating a risk of metastatic disease. Metastatic spread to the medial iliac lymph node has been described.[48] However, in the present case, histological evaluation of the enlarged left medial iliac lymph node revealed no neoplastic cells. Preoperative thoracic radiographs also had no evidence of pulmonary metastasis. Based on limited literature reports, the rate of metastatic disease in SCT appears to be 2–8%.[1,49] However, metastatic spread of SCT has manifested up to 4 years after removal of the primary tumor.[50] For cases with metastatic disease, the prognosis should be considered poor.[48,51–54] For these reasons, and in light of significant concentrations of serum AMH concentrations remaining 3 weeks after surgical removal of the neoplastic testis, an appointment for tumor surveillance 3 months after surgery was recommended.

Learning points

- AMH is a useful endocrine diagnostic marker for identification of retained testis in canine patients and may assist in identifying SCT
- A precipitous decline in inhibin B to undetectable concentrations was observed after surgical removal of Sertoli cell-affected retained testis
- Effects of hyperestrogenism on hair follicle growth can mimic other more common conditions of alopecia. Additional diagnostic tests (preputial cytology, ultrasonography, and hormonal assays) may assist in timely and accurate diagnosis of SCT
- The spermatic cord along with the affected testis should be submitted for histologic analysis. Identification of tumor emboli in cord vessels may guide prognosis and follow-up tumor surveillance

Conflict of interest

Authors have none to declare.

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