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Case Report Rapport de cas

Management of an invasive and metastatic Sertoli cell tumor with associated myelotoxicosis in a dog

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Abstract — We describe the surgical and post-operative management of a large, invasive, and metastatic functional Sertoli cell tumor in a 9-year-old cryptorchid male Labrador retriever dog. Despite residual disease after surgery, bone marrow recovery occurred without administration of bone marrow stimulants and serum estradiol accurately predicted tumor recurrence.

Résumé — Gestion d'une tumeur à cellules de Sertoli invasive et métastatique avec une myélotoxicose secondaire chez un chien. Nous décrivons la gestion chirurgicale et postopératoire d'une tumeur à cellules de Sertoli fonctionnelles, de grande taille, invasive et métastatique chez un chien Labrador retriever cryptorchide âgé de 9 ans. Malgré une maladie résiduelle après la chirurgie, le rétablissement de la moelle osseuse s'est produit sans l'administration de stimulants de la moelle osseuse et l'œstradiol sérique a fidèlement prédit la récurrence de la tumeur.

(Traduit par Isabelle Vallières)

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Sertoli cell tumors (SCT) are described as well-encapsulated and discrete, leading to relatively simple surgical excision and rare reports of tumor recurrence (1–12). Metastasis is identified in less than 15% of SCT at the time of diagnosis or up to 4 y after removal of the primary tumor (2,4,6–8,10,13,14). The prognosis for dogs experiencing metastasis of this type of tumor is extraordinarily variable, ranging from 5 d to more than 31 mo (2,4,6–8,10,14). The surgical management, postoperative monitoring, and outcomes specifically for the less common, larger, more invasive and metastatic SCT are generally not described (7,8,10).

In addition to the morbidity that can be associated with the physical presence of the mass and its metastases, estrogen myelotoxicity can occur in dogs with SCT and is associated with a guarded prognosis for bone marrow recovery even after castration (3,5,9,11,12). Recovery even with supportive care and bone marrow stimulants is unpredictable, with dogs either showing improvement in hematologic values within 2 to 3 wk, or succumbing to complications such as sepsis, hemorrhage, or anemia (3,5,11,15–17). In a series of 4 dogs with aggressive testicular tumors, the surgical management was only briefly outlined, and while locally invasive and metastatic, none of these tumors were functional (4). Herein, we describe the management of a large, hormonally functional, invasive, and metastatic SCT.

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Case description

A 9-year-old, cryptorchid male Labrador retriever dog was referred to the University of California-Davis William R. Pritchard Veterinary Medical Teaching Hospital for evaluation of a large intra-abdominal and a left inguinal mass. The patient was presented to the referring veterinarian 3 wk earlier for complaint of lethargy, decreased appetite, and a firm, rapidly growing mass in the left inguinal region. A complete blood (cell) count (CBC) performed at a commercial laboratory (Sysmex XT 2000iv; Sysmex, Kobe, Japan) revealed a marked leukocytosis characterized by a neutrophilia, left shift, and a moderate thrombocytopenia (20 days pre-op; Table 1). In addition, a lymphocytosis [15 830 cells/μL; reference interval (RI): 1000 to 4800 cells/μL], and monocytosis (7915 cells/μL; RI: 150 to 1350 cells/μL) were detected. Serum biochemistry revealed no clinically significant abnormalities. An abdominal ultrasound revealed a large intra-abdominal mass that appeared to communicate with the left inguinal mass through the inguinal ring. An exploratory laparotomy and incisional biopsy were performed at the referring clinic, and histopathology was reportedly consistent with either an SCT or adrenal neoplasia.

At presentation the patient was alert with normal vital signs. The abdomen was tense and moderately distended and discrete abdominal structures could not be palpated. A 15-cm firm, fixed mass was present in the left inguinal region. The patient also had slightly enlarged nipples and linear preputial erythema.

Table 1. Relevant complete blood cell count values over time

	20 days pre-op	1 day pre-op	12 days post-op	29 days post-op	47 days post-op	75 days post-op	125 days post-op
HCT (RI: 40% to 55%)	42%	32%	23%	20%	31%	38%	32%
Reticulocyte count (RI: 7000 to 65 000 cells/μL)	63 000	27 500	41 400	36 200	80 500	NA	40 000
WBC (RI: 6000 to 13 000 cells/μL)	158 300	9520	2280	2864	8200	12 710	37 380
Neutrophils (RI: 3000 to 10 500 cells/μL)	129 806	8187	1265	1862	5986	10 130	29 904
Bands (RI: rare)	4749	286	0	0	0	0	748
Platelets (RI: 150 000 to 400 000/μL)	50 000	17 000	7000	9000	29 000	229 000	181 000
Estradiol (pg/mL; intact male RI: 10 to 30 pg/mL; castrated RI: < 18 pg/mL)	NA	145	11	34	32	56	NA

Pre-op — prior to surgery; Post-op — after surgery; HCT — hematocrit; WBC — white blood cells; RI — Reference interval; NA — Not available.

Significant hematological changes (ADVIA 120; Siemens Healthcare Diagnostics, Tarrytown, New York, USA) included a mild normocytic, normochromic non-regenerative anemia, normal white blood cell count, and differential and a marked thrombocytopenia (1 day pre-op, Table 1). Clinically significant biochemical values (Roche Hitachi 917; Roche Diagnostics, Indianapolis, Indiana, USA) identified at this visit were hypoalbuminemia (21 g/L; RI: 34 to 43 g/L) and hyperglobulinemia (37 g/L; RI: 17 to 31 g/L). The activated partial thromboplastin time was slightly elevated (13.4 s; RI: 10.4 to 12.9 s), fibrinogen was moderately elevated (20.8 μmol/L; RI: 3.2 to 9.1 μmol/L), and D-Dimers were mildly elevated (196 ng/mL; RI: 0 to 186 ng/mL). The serum estradiol concentration was markedly elevated at 145 pg/mL (intact male RI: 10 to 30 pg/mL). Bone marrow aspirate cytology had rare mature megakaryocytes scattered singly across the samples, consistent with marked megakaryocytic hypoplasia. The erythroid lineage showed orderly maturation, with increased numbers across the smears. The granulocytic line was adequate with orderly maturation, and occasional giant bands interpreted as granulocytic dysplasia. The granulocytic:erythroid ratio was 1 to 2.5:1 based on a 500 cell differential (Figure 1).

Thoracic radiographs showed no evidence of pulmonary metastasis. Abdominal ultrasound and computed tomography (CT) confirmed a large lobulated, highly vascular mass that extended from the left inguinal region, through the inguinal ring, and throughout the peritoneal cavity up to the caudal aspect of the right ventral liver (Figure 2). The mass was highly cystic and heterogeneously contrast-enhancing. In the left caudal sublumbar region an additional mass with the same appearance and contrast enhancement pattern displaced the aorta and caudal vena cava ventrally and to the right. This mass extended cranially to abut the main body of the abdominal mass. This hypaxial mass was interpreted as a massively enlarged left medial iliac lymph node, given the absence of a normal left medial iliac lymph node. The left ureter traversed through a nest of abnormal tortuous blood vessels feeding the mass, and was in close apposition to its ventrolateral margin. Enlargement of other abdominal lymph nodes was noted and normal left testicular tissue was absent.

A presumptive diagnosis of estrogen toxicity secondary to an SCT in an inguinal cryptorchid testicle was made. Understanding the risk of intraoperative hemorrhage due to severe thrombocytopenia and the guarded long-term prognosis due to myelosuppression, the owners elected to proceed with attempted surgical removal of the mass. Client finances limited the use of blood products, but the patient was transfused with 1 unit of platelet concentrate (Animal Blood Resources International, Dixon, California, USA) IV and administered desmopressin (DDAVP Injection; Sanofi US, Bridgewater, New Jersey, USA) 1 μg/kg body weight (BW), SQ before surgery. A midline celiotomy incision deviating to the left of the prepuce and over the left inguinal region was performed to expose both the intra- and extra-abdominal portions of the mass. The mass tracked from the subcutaneous inguinal region, through the inguinal ring, and along the apparent testicular artery and vein extending to the caudal pole of the left kidney. The intra-abdominal portion of the mass was enormous, highly vascular, and multi-lobulated, and was adhered to the left ureter and caudal pole of the kidney (Figure 3). The inguinal portion of the mass was dissected from subcutaneous attachments and passed through the inguinal ring into the abdomen so that the mass could be removed *en bloc.* The enlarged left medial iliac lymph node was visualized lateral to the aorta. *En bloc* removal of this metastatic lymph node was attempted, but aborted due to continued hemorrhage associated with dissection from the hypaxial musculature and the patient's packed cell volume and total protein decreasing to 22% and 52 g/L, respectively, during the course of the procedure. After removal of all other vascular attachments, and careful isolation from other visceral structures, the mass was ligated and transected at the narrowest isthmus of attachment to the enlarged left medial iliac lymph node. The expansile defect in the inguinal ring created by extension of the mass through it and into the abdomen was reconstructed with simple interrupted sutures of 2-0 PDS to prevent future visceral herniation, and the ventral midline

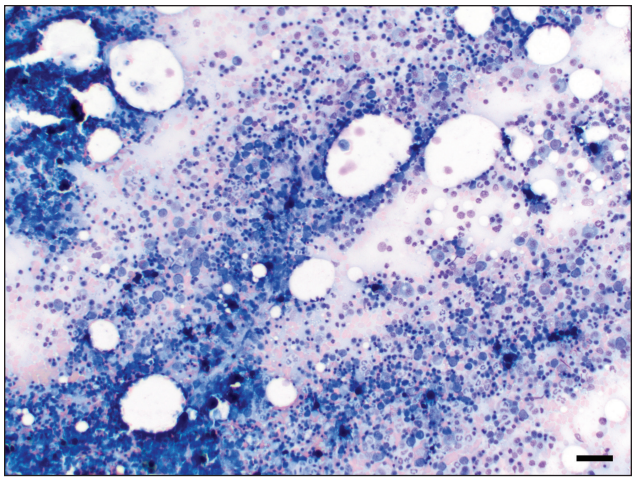

Figure 1. Representative cytology of a bone marrow aspirate just prior to surgical excision of the presumed SCT. Many unit particles were present (upper and lower left of image) that were hypercellular due to erythroid hyperplasia and granulocytic dysplasia, and contained increased iron. No megakaryocytes are visible in the image; however, occasional megakaryocytes were noted individually along the periphery of the smear, consistent with marked megakaryocytic hypoplasia. Wright-Giemsa stain. Magnification = 100×. Scale bar = 50 μm.

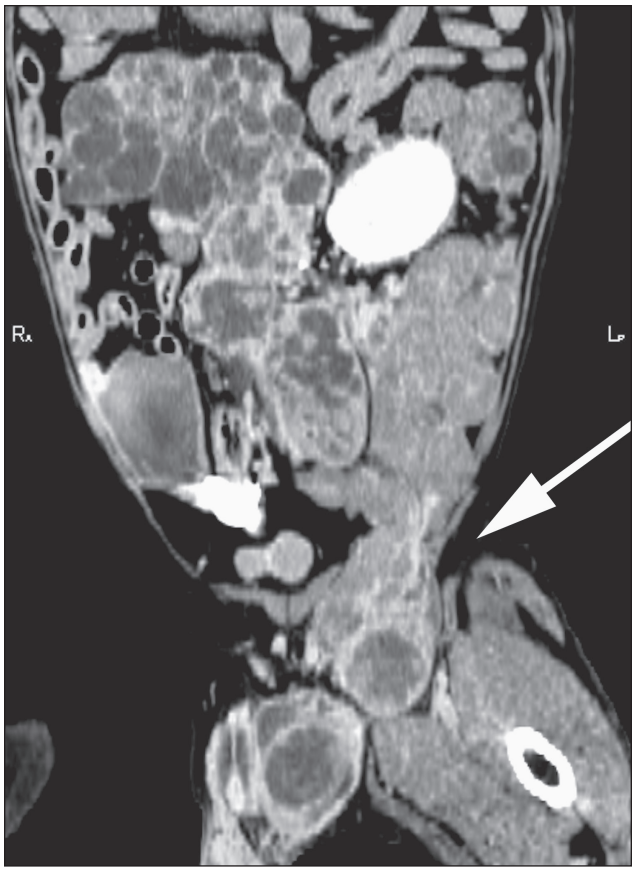

Figure 2. Contrast-enhanced CT image showing an oblique coronal view of the mass invading through the inguinal ring and into the abdomen from the subcutaneous space in the inguinal region (white arrow).

celiotomy was closed. The right testicle was removed via closed castration with a standard pre-scrotal approach. The patient made an uneventful recovery. Moderate parapreputial, inguinal, and abdominal bruising was noted postoperatively. The patient was discharged with instructions for strict exercise restriction and vigilant monitoring for signs of bleeding. Amoxicillin/clavulanic acid (Zoetis, Kalamazoo, Michigan, USA) 12.8 mg/kg BW, PO, q12h, and tramadol (Amneal Pharmaceuticals, Hauppauge, New York, USA), 1.3 to 2.6 mg/kg BW, PO, every 8 to 12 h as needed for pain, were prescribed at discharge.

Histopathology of the mass confirmed the diagnosis of SCT. Anisocytosis and anisokaryosis were moderate and 4 mitotic figures were seen in 10 high power (400×) fields. Numerous small nodules expanded beyond the testicular capsule and spread along local lymphatics. An intratubular seminoma was present within the right testicle. The patient was monitored postoperatively via serial physical examinations, CBCs, and estradiol levels in order to track the progression of estrogen toxicity (Table 1). Postoperative adjunctive chemotherapy was discussed with the clients, but declined due to the risks of exacerbating the myelosuppression and the uncertain benefit. Despite residual gross disease remaining, the serum estradiol concentration had decreased dramatically 12 d after surgery to within normal limits.

Amoxicillin/clavulanic acid was continued due to progressive neutropenia, which reached a nadir of 1265 cells/μL 12 d after surgery. The platelet count also reached its lowest value of 7000/μL at this time. A non-regenerative anemia was continuing to worsen by day 29 with a hematocrit of 20%. Bone marrow cytology was repeated on day 29, with marked hypocellularity of unit particles secondary to severe megakaryocytic and granulocytic hypoplasia (Figure 4). The erythroid series was present with orderly maturation, with this response considered inadequate, given the established anemia. The granulocytic:erythroid ratio was markedly decreased at 1:20.

Forty-seven days after surgery a recheck CBC showed the initial signs of bone marrow regeneration with an increased hematocrit, neutrophil concentration, platelet concentration, and reticulocytosis. Amoxicillin/clavulanic acid was discontinued at this time. A persistent but mild non-regenerative anemia and a normal platelet concentration were present throughout the remainder of the follow-up period. With stabilization of the hematologic parameters, a second exploratory laparotomy to attempt removal of the tumor-infiltrated medial iliac lymph node was offered, but declined.

At recheck evaluation 75 d after surgery, the serum estradiol concentration was found to have increased to 56 pg/mL and abdominal ultrasound confirmed a lobular mass extending from the spleen, along the aorta and caudal vena cava to the region of the urinary bladder and prostate. Separate spherical masses were detected in the region of the sublumbar lymph nodes and within the caudal pole of the left kidney, extending through the parenchyma into the renal pelvis. These findings were consistent with tumor recurrence and further metastasis.

On day 125 the abdominal mass was again palpable, and extended from the cranial abdomen towards the bladder. Preputial erythema, a pendulous prepuce, and mild gynecomastia were also evident at this visit. By day 166, the dog

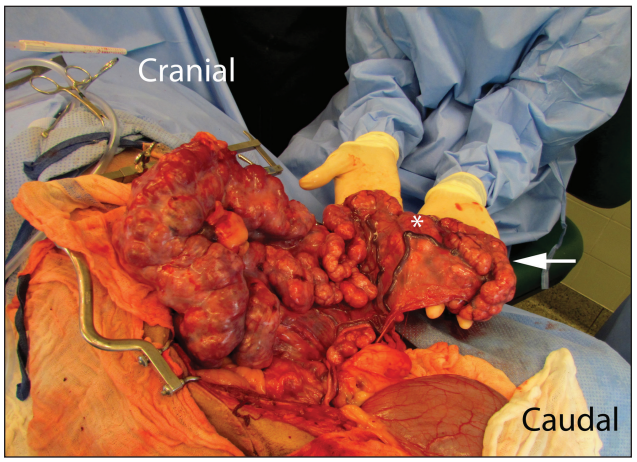

Figure 3. Intraoperative image showing the SCT extending up to the liver. The inguinal portion of the mass has been dissected away from the subcutaneous tissue and remains attached to the large intra-abdominal portion (arrow). An asterisk (*) delineates the portion of the mass that passed through the inguinal ring.

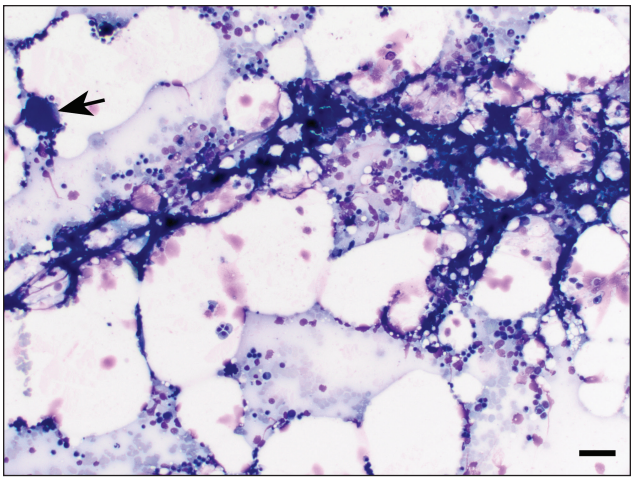

Figure 4. Representative cytology of a bone marrow aspirate from a dog 29 days after initial diagnosis of SCT and estrogen toxicity. Many unit particles were present that were hypocellular due to marked megakaryocytic and granulocytic hypoplasia. Rare megakaryocytes were present (arrow). Wright-Giemsa stain. Magnification = 100×. Scale bar = 50 μm.

had developed anorexia, lethargy, straining to defecate, and a markedly distended abdomen. Physical examination identified a palpable firm mass occupying most of the abdomen both cranially and caudally and the dog appeared jaundiced. Euthanasia was elected at this time due to his poor quality of life and grave prognosis. The owners did not authorize a necropsy and no additional blood was drawn before euthanasia.

Discussion

There are numerous reports of testicular SCT in the literature but these either describe the post-surgical outcome after excision of relatively well-encapsulated and discrete tumors, or they do not specifically describe the management of the less common large and invasive tumors mentioned within series (1–12). One report, however, did describe an invasive seminoma that originated from a testicle in the inguinal region and invaded through the inguinal canal and into the surrounding body wall (4). The case management details for treatment of the less common, aggressive SCT have not been described until now. Here we outlined the potential for damage to vital structures such as the ureter and kidney due to close association with the tumor when attempting removal. In addition, the impressive vascularity and invasiveness of the mass made complete surgical removal impossible when compounded by the concurrent thrombocytopenia.

Hyperestrogenism is commonly observed secondary to SCT: up to 57% of affected dogs show signs of hormonal imbalance (7,8,10). Almost all dogs displaying clinical signs of elevated estrogen levels have alopecia with or without signs of feminization such as gynecomastia, galactorrhoea, atrophied penis, pendulous and edematous prepuce, and attraction to other male dogs (3,5–12). Hyperestrogenism is also presumed to underlie the development of linear preputial erythema in dogs with SCT, although the exact etiology of this sign remains obscure (18,19). In our report, the estradiol concentration at presentation was almost 5 times the upper limit of normal for an intact dog, and while alopecia was not observed there were mild signs of feminization including prominent nipples and linear preputial erythema. While seminomas have uncommonly been implicated in the etiology of hyperestrogenism, the incidental finding of a seminoma was unlikely the cause in our patient, as evident by the re-elevation of estradiol levels with recurrence of the SCT (3,20,21).

Myelotoxicity is a less commonly recognized potential sequela of hyperestrogenism, and both endogenous (testicular or adrenal neoplasia) and exogenous (medication) sources have been implicated (3,5,7,9,11,12,15). Some evidence suggests that estrogen does not have a direct effect on bone marrow but rather stimulates thymic tissue to produce a myelopoiesis inhibiting factor (22,23). The exact mechanism of bone marrow toxicity is unclear but the end result is death of hematopoietic stem cells, with individual dogs varying in susceptibility (22,24,25). Within the first 3 wk of experimental toxicity, a leukocytosis characterized by a left-shifted neutrophilia is detected, which may then be followed by severe neutropenia. A non-regenerative anemia and thrombocytopenia are often progressive throughout these 2 phases. The final phase either sees recovery of circulating cell counts, or aplastic anemia and death (22,24–26). In the bone marrow, the initial phase is characterized by an elevated granulocytic:erythroid ratio and if this is followed by neutropenia in the second phase, a decreased granulocytic:erythroid ratio is then present (25). Megakaryocyte numbers decrease throughout the first 2 phases. In 1993, Farris and Benjamin (22) theorized that the neutrophilia seen in affected dogs may be a consequence of the inflammatory response to foci of bone marrow necrosis observed after high doses of estrogen. The highest white blood cell count reported in this context is 119 500/μL, recorded in a dog experimentally treated with 100 mg of diethylstilbestrol dipropionate, PO, daily. To the authors' knowledge there are no previously published reports of neutrophilia in cases of definitive endogenous estrogen toxicosis (3,5,9,11). There are, however, 4 dogs reported with signs of feminization

which also displayed a mild leukocytosis between 17 000/μL and 33 000/μL (6,12,14). The clinical case reported here is unique in the finding of a dramatic left-shifted neutrophilia of 129 800/μL, quickly followed by a progressive pancytopenia induced by endogenous estrogen production, which neatly mirrors prior reports of experimentally induced estrogen toxicosis.

It is clear from the literature that estradiol concentration may not be the sole determinant for development of feminization and bone marrow toxicity (3,11). Signs of feminization may be more associated with a decreased testosterone/estradiol ratio than with elevation of the estradiol concentration alone, or may reflect secretions of other forms of estrogen and estrogenic substances that are not routinely tested for (20). In our report, however, serum estradiol alone functioned as an accurate biomarker for monitoring of this aggressive SCT, as evident by the normalization of this value after massive debulking of the tumor and the gradual increase in concentration with recurrence and further metastasis. Estradiol concentration is well-described as a valuable initial diagnostic in dogs with SCT, but is inconsistently reported as a postoperative monitoring tool (3,5,7,8). In 4 previously reported cases, serum estradiol concentrations were measured before and 2 to 4 wk after surgical excision of primary or metastatic tumors and found to have decreased from an elevated level before surgery to within the normal range, but these cases were not followed further (11,12,14).

The dog herein received supportive care consisting of a single unit of platelet concentrate and an injection of desmopressin before surgery, followed by antibiotics and pain medications after surgery. Given that very few testicular tumors in dogs display clinical evidence of malignancy, there are few published reports on the efficacy of adjuvant therapy for these more aggressive tumors and no current standard treatment recommendations (4). Several previous reports have, however, advocated the use of a three-pronged approach to support bone marrow recovery in dogs with estrogen toxicity. After removing the source of estrogen, therapy consists of blood products to alleviate anemia and support platelet numbers, antibiotics to avoid neutropenic sepsis, and bone marrow stimulants including lithium and androgens (3,5,11,15–17). Both androgens and lithium are used in human medicine for treatment of bone marrow failure of various etiologies but evidence of their efficacy in dogs with estrogen toxicity is weak and limited to case reports only (27,28). In 2 small retrospective studies describing dogs with endogenous estrogen toxicity, recovery was observed in 2 of 10 dogs and 2 of 8 dogs, with treatment being inconsistent but including that described above (3,5). In dogs that recover from estrogen toxicity, improvement in hematologic values is evident within 2 to 3 wk but complete recovery often takes several months (3,5,15). We were limited in the amount of blood products that we could administer to the dog of this report due to client cost constraints, but with just antibiotic treatment long-term, the dog showed signs of regeneration on a CBC 47 d after surgery, and recovery was complete by day 75. The lack of bone marrow stimulant administration in our patient may have resulted in a delay in bone marrow recovery. It is also possible that the severity of bone marrow toxicosis, as determined by the dose of estrogen and individual patient sensitivity, determines the rate of recovery. Therefore, this report suggests that simple supportive care to combat the consequences of pancytopenia and regular monitoring may be sufficient in some dogs with estrogen toxicity to enable bone marrow recovery over time.

Here we have described for the first time in detail the surgical debulking of a large, invasive and metastatic functional SCT, postoperative management with antibiotics alone, the successful, albeit temporary, recovery from bone marrow hypoplasia with supportive care over a longer time course, and the use of serial serum estradiol levels for disease monitoring. Despite residual disease remaining *in situ* after surgery, estradiol levels decreased transiently back to normal, which was accompanied by mitigation of bone marrow hypoplasia and a good quality of life until shortly before euthanasia almost 6 mo later. Although pancytopenia from estrogen-induced myelotoxicity still carries a guarded prognosis, this case demonstrates that attempted removal of estrogen secreting tissue is warranted and may be curative if all neoplastic tissue is excised. Supportive care only, without the addition of bone marrow stimulants may be adequate to allow recovery in some dogs, and serial serum estradiol concentrations may serve as a helpful biomarker in monitoring disease progression in high-risk cases. CVJ

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