

Feminization and severe pancytopenia caused by testicular neoplasia in a cryptorchid dog

Feminisatie en ernstige pancytopenie veroorzaakt door testiculaire neoplasie in een cryptorche hond

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ABSTRACT

In this case report, a paraneoplastic syndrome caused by testicular neoplasia in a ten-year-old cryptorchid dog is described. Feminization and pancytopenia were observed, resulting from the testicular neoplastic production of estrogens. A diagnosis of testicular tumor and associated bone marrow suppression was made by ultrasonography and blood examination, with estrogen blood levels being severely elevated. Urinalysis revealed a urinary tract infection. Castration was performed together with a blood transfusion, and antibiotic treatment was started. After an initial improvement, the dog died suddenly after approximately three weeks.

In this report, the importance is highlighted of identifying clinical signs associated with feminization in intact male dogs at an early stage, to avoid severe, potentially irreversible, hematological consequences due to bone marrow suppression. Elective orchidectomy of both testes is highly recommended in cryptorchid dogs as neoplastic transformation of the undescended testis may occur, with potentially fatal outcome.

SAMENVATTING

In deze casuïstiek wordt een paraneoplastisch syndroom beschreven veroorzaakt door een testistumor bij een tien jaar oude, cryptorche hond. Feminisatie en pancytopenie werden gezien als gevolg van de productie van oestrogenen door het testiculaire neoplastisch proces. De diagnose van testistumor en geassocieerde beenmergsuppressie werd gesteld door middel van echografie en bloedonderzoek, waarbij de oestrogeenbloedspiegel sterk gestegen was. Urineonderzoek toonde een urineweginfectie aan. De hond werd gecasteerd, kreeg een bloedtransfusie en werd behandeld met antibiotica. Na een initiële verbetering stierf de hond onverwacht, ongeveer drie weken na het stellen van de diagnose.

In deze casus wordt benadrukt dat tekenen van feminisatie tijdig opgemerkt dienen te worden bij intacte, mannelijke honden en dit om erge, mogelijk irreversibele, hematologische gevolgen door beenmergsuppressie te vermijden. Electieve castratie van beide testes is sterk aangeraden bij dieren met cryptorchidie omdat neoplastische transformatie van de niet-afgedaalde testis kan optreden, mogelijk met een fatale uitkomst.

INTRODUCTION

Testicular tumors are the second most common neoplastic conditions of intact male dogs (Lawrence and Saba, 2013), with a prevalence varying from 0.9 to 16.8%, and represent more than 90% of all tumors involving the male genital system (Grieco et al., 2008; Liao et al., 2009; Lopate, 2010). The three most common types of testicular neoplasia in dogs are Sertoli cell tumors, seminomas and interstitial cell tumors,

which represent 8-44%, 31-41% and 25-50% of all testicular tumors, respectively (Lopate, 2010; Sanpera et al., 2002; Kim and Kim, 2005; Kang et al., 2011; Grieco et al., 2008). In approximately 7% of canine testicular neoplasms, mixed tumors are found in the same testicle (Patnaik and Mostofi, 1993). Sertoli cell tumors mostly occur in the undescended testis of cryptorchid dogs, whereas interstitial cell tumors and seminomas are more frequently seen in the descended testis (Lopate, 2010). Canine cryptorchidism has an



Figure 1. The dog was presented with a thin haircoat and greasy skin. Gynecomasty and developing mammary glands, hyperpigmentation and a pendulous prepuce were visible on the ventral abdomen (picture insert).

incidence of approximately 1.2 to 5% (Johnston et al., 2001) with the right testicle being affected more commonly (Plavec et al., 2007), and the incidence of testicular neoplasia is much greater in cryptorchid testes than in normally descended testes. The risk for Sertoli cell tumors and seminomas is respectively 26 and 15 fold higher in cryptorchid dogs (Hong et al., 2011). In a recent study performed on cryptorchid dogs, a higher incidence of seminomas in inguinal and Sertoli cell tumors in abdominal testicles is described (Ciaputa et al., 2012).

Testicular neoplasms are usually benign, but some have malignant characteristics. For Sertoli cell tumors, metastatic rates of 2-14% have been described (Lopate, 2010; Hong et al., 2011). Metastases of these tumors usually occur to regional lymph nodes or organs, such as the kidneys, pancreas, lungs or spleen (Johnston et al., 2001). Seminomas are known to metastasize to the regional lymph nodes in 15% of cases and distantly in 6-10% of cases, (Johnston et al., 2001; Lopate, 2010). Interstitial cell tumors on the other hand are almost always benign (Lopate, 2010).

Dogs with testicular tumors may develop paraneoplastic syndromes, and this is mostly seen in association with Sertoli cell tumors. Neoplastic cells within testicular tumors may produce estrogen and/or testosterone, resulting in excessive hormonal concentrations. Indeed, the sustentacular cells of Sertoli contain large amounts of estrogen, especially in the dog (Huggins and Moulder, 1945). Hyperestrogenism leads to feminization of the male individual, which is observed in 25-50% of dogs with Sertoli cell tumors, in 5% of dogs with interstitial cell tumors, and uncommonly in cases with seminoma (Johnston et al., 2001; Sanpera et al., 2002; Kim and Kim, 2005; Lopate, 2010). Hyperestrogenism leads to clinical signs, such as bilateral symmetrical alopecia, hyperpigmentation, gynecomastia, pendulous prepuce, linear preputial erythema, squamous metaplasia of the prostate gland and attraction of male dogs. Bone marrow hypoplasia, resulting in pancytopenia, may also be

seen as a consequence of hyperestrogenism. (Feldman and Nelson, 2004; Lopate, 2010). High concentrations of testosterone have been reported in dogs with interstitial cell tumors and may lead to prostatic disease, perianal adenoma, perianal gland hyperplasia and perineal herniation (Johnston et al., 2001; Sanpera et al., 2002; Plavec et al., 2007; Grieco et al., 2008; Lopate, 2010; Ciaputa et al., 2012).

In this case report, the occurrence of a paraneoplastic syndrome is described, more specifically, feminization and pancytopenia in a cryptorchid dog with testicular neoplasia. The diagnostic approach and therapeutic management of dogs with testicular tumors and the differential diagnosis of pancytopenia are discussed.

CASE REPORT

A ten-year-old, male Yorkshire terrier was presented at the emergency service of the Small Animal Department of Ghent University with complaints of lethargy, anorexia, vomiting, fever and a tense abdomen since three days. The referring veterinarian performed a blood examination that revealed pancytopenia (leukopenia, non-regenerative anemia and thrombocytopenia), mild hyponatremia, mild hypokalemia and mildly increased serum urea concentration (Table 1). Abdominal ultrasonography revealed a mass in the caudal abdomen. The dog was known to be bilateral cryptorchid, with the right testicle in abdominal and the left testicle in inguinal position. The dog was referred for further diagnostic testing and treatment.

On physical examination, the dog was quiet, alert and responsive, with a body temperature of 39.3°C. Mucous membranes were mildly tacky and pale pink. The dog was cardiovascularly stable, but mildly dehydrated. Abdominal palpation revealed abdominal pain, making deep palpation impossible. Further clinical examination revealed a pendulous prepuce, gynecomasty, enlarged mammary glands, hyperpigmented maculae (macular melanosis), a thin haircoat and greasy skin. These findings were suggestive of feminization (Figure 1).

Complete blood count was repeated and showed severe leukopenia, due to neutropenia and eosinopenia (Table 1), moderate non-regenerative normocytic, normochromic anemia and severe thrombocytopenia. These abnormalities were confirmed by microscopic examination of a blood smear.

Urine was collected by cystocentesis during initial ultrasonographic examination. Urinalysis revealed pyuria, hematuria and proteinuria (urinary protein: creatinine ratio 1.67; reference value < 0.50). Urine bacterial culture revealed growth of *Sphingomonas (Pseudomonas) paucimobilis*, but the bacterial growth was too slow to obtain an antibiogram. The observed proteinuria was most likely postrenal in origin, secondary to the bacterial cystitis. Although an uncompli-

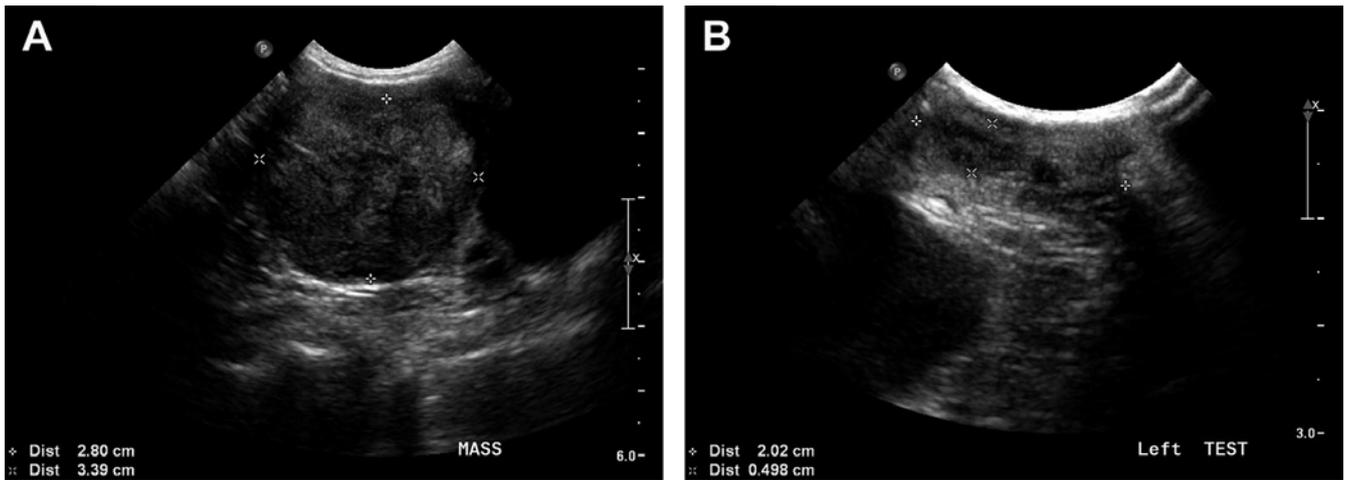


Figure 2. Ultrasonographic images of the dog. **A.** In the abdomen, a mass was detected, which was identified as the right testicle. **B.** The left testicle was normal in size, but located in the inguinal region.

cated urinary tract infection is not associated with fever, a concurrent bacterial prostatitis that is frequently noticed in intact, male dogs with urinary tract infection could explain the fever. Secondly, a pyelonephritis could not be excluded, but increased serum creatinine concentration or evidence of tubular damage (e.g. glucosuria, tubular casts) was lacking.

On abdominal ultrasonography, the liver was normal in size and sharply delineated, but there were multiple ill-defined hypoechoic nodules and one hyperechoic nodule, which could be compatible with degenerative changes, hyperplasia, regeneration or neoplasia. Mineralization of the liver parenchyma was also present and the gall bladder showed a small amount of sludge. Adrenal glands were normal in size, but moderately irregular and hypoechoic. The prostate was normal in size and smoothly delineated, but the parenchyma was heterogeneous, with the presence of multiple cysts and mineralization, which could be consistent with a concurrent prostatitis. The right testicle was located in the abdomen and severely enlarged (Figure 2A). The left testicle was located in the inguinal region, was normal in size and contained one hypoechoic nodule in the cranial pole (Figure 2B). The diagnosis of bilateral cryptorchidism was confirmed. Finally, the kidneys were normal in size and shape and showed no ultrasonographic evidence of pyelonephritis.

Estradiol concentrations were measured, using a rapid immunoassay, and the results indicated hyperoestrogenemia (55.2 pg/mL; reference values for intact male dogs: < 25 pg/mL). Clotting times (prothrombin time (PT) and activated partial thromboplastin time (aPTT)) were assessed and revealed a slight prolongation of aPTT (131 seconds; reference interval 72-102 seconds).

Thoracic radiographs (left-right and right-left lateral, ventrodorsal images) were performed to check for metastases. A focal, ill-defined (3 x 2 cm) interstitial pattern was seen at the dorsal aspect of the caudal lung field in the region of the 9th-11th intercostal

spaces (Figure 3). Pleural fissure lines were present between both parts of the left cranial lung lobes and between the right middle and caudal lung lobes. The significance of the interstitial lesion was unclear and differential diagnosis included pathology in transition (e.g. lung edema or pneumonia), neoplasia and pulmonary thromboembolism. No signs of metastases could be detected.

After the diagnosis was made, the dog was hospitalized (in total six days) in the intensive care unit. He was treated with lactated Ringer's infusion (B. Braun Melsungen AG, Germany), cefazolin (Cefazoline® 1g, Sandoz, Switzerland, 20 mg/kg, q12h), ranitidine hydrochloride (Zantac® 50 mg/2 mL, Glaxo Smith Kline, Belgium, 2 mg/kg) and analgesia. The analgesia consisted of methadone (Comfortan®, Eurovet, Belgium, 0.2 mg/kg, q4h) and lidocaine (Xylocaine® 2%, Astrazeneca, Belgium, bolus of 2 mg/kg, followed by a continuous rate infusion (CRI) of 30 µg/kg/min). Ketamine (Anesketin® 115 mg/mL, Eurovet, Belgium, 1 mg/kg, q4h) was added to the therapy later on and lidocaine was increased to 50 µg/kg/min because of persistent abdominal pain. Because of per-

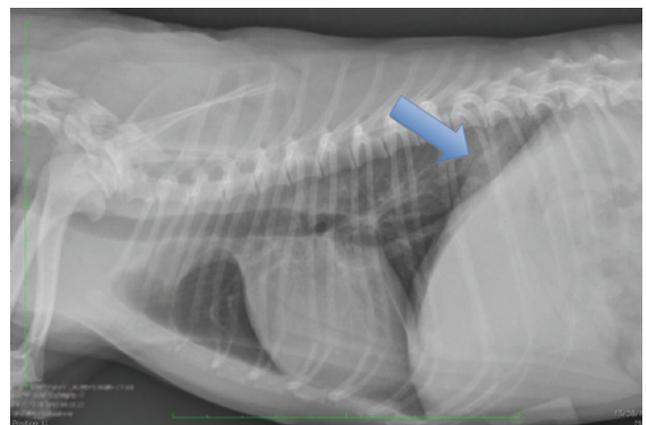


Figure 3. Left lateral radiography of the thorax. An ill-defined interstitial pattern is present in the caudal lung lobe (arrow).

sistent fever, enrofloxacin (Baytril® 2.5%, Bayer, Germany, 5 mg/kg, q24h) was added to the therapy during the first night. To avoid hospital-acquired infections, the hospitalization personnel and students were advised to handle the patient as hygienically as possible (gloves, washing and antiseptics on hands) because of the presence of severe neutropenia.

The second day, the dog was found to be dull and hypothermic most likely due to side effects of the analgesic drugs that were necessary to control the abdominal pain. Hypothermia and lethargy in a neutropenic dog could also be due to a septic process, such as septic peritonitis, but the dog did not present other signs compatible with sepsis. Furthermore, the dog continued to have abdominal discomfort, despite the administration of multi-modal analgesia. Therefore, it was decided to perform surgery for castration and liver biopsy. Before surgery, a fresh blood transfusion was carried out (20 mL/kg), because of the presence of anemia, thrombocytopenia and a slightly prolonged aPTT. The dog was premedicated with methadone (Comfortan® 10 mg/mL, Eurovet, Belgium; 0.3 mg/kg) and midazolam (Dormicum® 15mg/3mL, Roche, the Netherlands; 0.3 mg/kg). Anesthesia was induced with fentanyl (Fentadon® 50 µg/mL, Eurovet, Belgium, 70 µg/kg), and maintained with isoflurane in oxygen (Isoflo®, Abbott laboratories Ltd., United Kingdom (UK)). During surgery, the dog received a CRI of fentanyl (5 µg/kg/h). The undescended abdominal right testicle was located lateral to the corpus of the bladder and the left testicle was atrophied and had an inguinal position. After castration, inspection of the abdomen also showed a subjectively enlarged liver with multiple small yellow masses (< 1mm) located underneath the liver capsule. Cranial to the right kidney, a yellow and nodular area was seen in the caudate lobe and the right lateral lobe of the liver. Biopsies were taken from this mass, the draining lymph node (celiac lymph node) and other affected parts of

the liver. Both testicles, the liver biopsies and lymph node were sent for histopathological examination. After surgery, the infusion therapy, a CRI of lidocaine (50 µg/kg/min), and methadone (0.2 mg/kg q4h) were continued. The dog appeared less painful on abdominal palpation, so ketamine was not reinstated.

During the third day of hospitalization, maropitant (Cerenia® 10 mg/mL, Pfizer, UK, 1 mg/kg) was added to the treatment because the dog appeared nauseated. On day four, a nasoesophageal feeding tube was placed because of persistent anorexia. In addition, potassium supplementation was initiated because of developing hypokalemia (Kali-sterop® 3g/10 mL, Sterop, Belgium, 30 milliequivalents/L), resulting in rapid normalization of serum electrolyte concentrations.

During hospitalization, the infusion rate and analgesia were regularly adjusted based on clinical parameters and abdominal pain. Hematological values (CBC, blood smear, manual hematocrit) were also monitored (Table 1). The amount of thrombocytes varied between 0 thrombocytes per high power field (HPF) at arrival and 3 to 5 thrombocytes per HPF during follow-up in the hospitalization. On the third day of hospitalization, small thrombocyte aggregates and mild polychromasia were detected. On the last day of hospitalization, several band neutrophils could be detected in the periphery, corresponding to a left shift in the blood.

After gradual tapering of the infusion rate and analgesia, the infusion therapy and lidocaine administration were stopped on day six because the dog started eating and because no pain could be elicited on abdominal palpation. Urinalysis was repeated and found to be negative for pathogenic bacteria. Medication was switched to oral treatment and the dog was discharged with the following treatment advice: enrofloxacin (Xeden®, Eurovet, Belgium, 5 mg/kg), tramadol hydrochloride (Tramadol EG® 50mg, Euro-

Table 1. Summary of the results of the complete blood count performed by the referring veterinarian and during hospitalization at the Small Animal Clinic of the Faculty of Veterinary Medicine, Ghent University.

	D-2	D1	D3	D4	D5	D7	D16	Reference interval RV	Reference interval Ghent University
Hemoglobin	10.9	9.7	12.5	13.4	12	12.4	11.8	14.0-20.0 g/dL	13.1-20.5 g/dL
Hematocrit	30.7	25.8	33	35.8	33.4	34.4	36.6	43.0-59.0 %	37.3-61.7%
Reticulocytes	0.4	12.6	10.5	10.1	14.5	20.4	0.4	%	10-110 x 10 ³ /µL
Leukocytes	3.0	2090	2180	2070	1690	2660	2300	6.0-16.0 x 10 ⁹ /L	5050-16760 x 10 ⁶ /L
Neutrophils	1950	40	90	60	870	1170	828	3000-11500 x 10 ⁶ /L	2950-11640 x 10 ⁶ /L
Lymphocytes	930	1200	1400	1630	580	840	1403	1000-4800 x 10 ⁶ /L	1050-5100 x 10 ⁶ /L
Eosinophils	0	0	10	10	10	10	0	< 1250 x 10 ⁶ /L	60-1230 x 10 ⁶ /L
Monocytes	120	850	680	370	230	640	69	<1350 x 10 ⁶ /L	160-1120 x 10 ⁶ /L
Basophils	0	0	0	0	0	0	0	0-100 x 10 ⁶ /L	0-100 x 10 ⁶ /L
Platelets	47	12	15	22	39	14	19	164-510 x 10 ³ /L	148-484 x 10 ³ /µL

D-2 = Blood examination performed by the referring veterinarian 2 days prior to hospitalization; D1-D7 = Blood examination performed during hospitalization at the Small Animal Clinic of Ghent University; D16 = Blood examination performed by referring veterinarian 10 days after discharge; ND = Not determined; Reference interval RV = Reference interval for blood examinations performed by the referring veterinarian; Reference interval Ghent University = Reference interval for blood examinations performed during hospitalization at the Small Animal Clinic of Ghent University

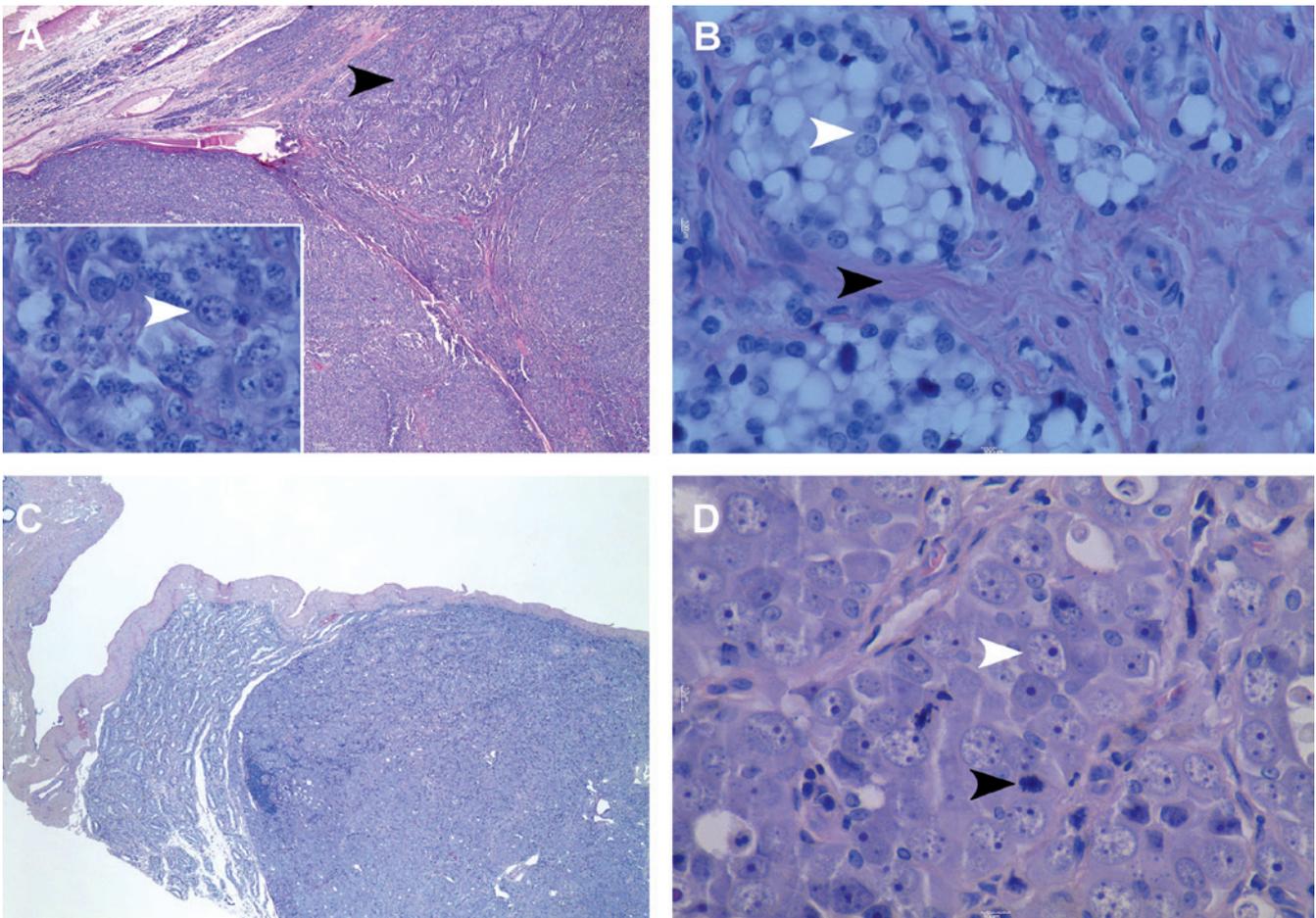


Figure 4. Images of the histology (hematoxylin-eosin stain) of the right (A, B) and left testicle (C, D). **A.** Overview of the seminoma in the largest right testicle. At the black arrow, remaining compressed tubules can be seen. The picture insert shows the neoplastic cells of the seminoma of the right testicle. These cells are large, irregular, round to oval cells with a moderate amount of basophilic, vacuolated cytoplasm and show mild anisocytosis and anisokaryosis. Large, round to oval and irregular nuclei (white arrow) containing 1 to 2 nucleoli and punctate chromatin can be observed. **B.** This image shows pockets of neoplastic cells of the Sertoli cell tumor, separated by eosinophilic fibrinous stroma (black arrow). The neoplastic cells (white arrow) are pleiomorphic with a small amount of basophilic, strongly vacuolated cytoplasm. **C.** Overview of the seminoma located in the smallest left testicle. Surrounding the nodular mass, the normal testicular parenchyma is atrophied. **D.** Detail of the neoplastic cells of the seminoma in the left testicle. The tumor cells (white arrow) are diffusely arranged, large pleiomorphic to round cells, with a moderate amount of basophilic cytoplasm and large, round basophilic nuclei with prominent nucleoli. There is a moderate anisokaryosis and a mitotic rate of 3-5 mitotic figures (black arrow) per high power field.

generics NV, Belgium, 3-5 mg/kg) and ranitidine (Zantac® 150 mg/10 mL, 2 mg/kg, q 8h). The owners were advised to return to their referring veterinarian for a follow-up examination and hematology after one week. Enrofloxacin was prescribed for three weeks, and a urinalysis was planned five days after termination.

Histopathological examination was indicative of a seminoma in both testicles, combined with a Sertoli cell tumor in the right testicle and severe atrophy of the left testicle (Figure 4). No signs of malignancy were detected in the samples taken from the liver nodules and lymph nodes. Histopathology of the liver was consistent with atrophy of the parenchyma and severe fibrosis.

Results of the hematology performed ten days after discharge are presented in Table 1. The dog died

unexpectedly at home, approximately three weeks after diagnosis. No necropsy was performed.

DISCUSSION

As illustrated by this case, dogs with paraneoplastic syndromes due to testicular tumors are often presented with vague complaints of anorexia and lethargy. On physical examination, signs of feminization, such as bilateral symmetrical alopecia, gynecomastia, pendulous prepuce and macular melanosis are present in many cases, but may remain unnoticed. Sometimes, the appearance of female behavior is the only symptom that is observed by the owner, for example taking a female position during urination (squatting) or attracting male attention. Often, a distended abdo-

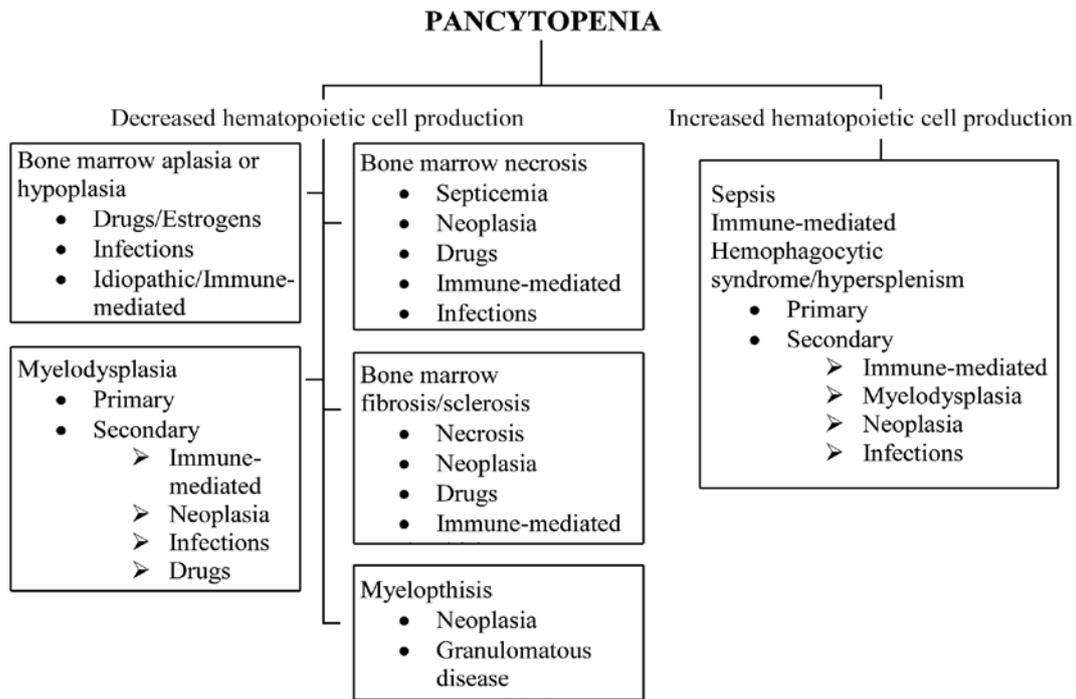


Figure 5. Summary of the causes of pancytopenia (Adapted from: Kearns and Ewing, 2006).

men is noticed and a mass is palpated in the abdomen or inguinal region. Some animals suffer from pyrexia, as happened in this case. This is mostly due to secondary infections, for example of the urinary tract, due to the presence of neutropenia (Dhaliwal et al., 1999; Sanpera et al., 2002; Kim and Kim, 2005; Plavec et al., 2007; De Bosschere and Deprest, 2010; Hong et al., 2011; Kang et al., 2011; Warland et al., 2011; Carreira et al., 2012; Herndon et al., 2012; Quartuccio et al., 2012).

The present case showed pancytopenia, namely a combination of non-regenerative anemia, leukopenia and thrombocytopenia, on complete blood count. General causes of pancytopenia can be divided into two groups: diseases that cause a decrease or an increase in hematopoietic bone marrow cell production (Kearns and Ewing, 2006; Sontas et al., 2009). The etiology of both groups is further illustrated in Figure 5. Estrogens are well known as suppressors of the bone marrow leading to decreased hematopoiesis, but the exact mechanism is still incompletely understood. They might have an effect on stem cell differentiation and iron utilization and possibly inhibit or stimulate the production of erythrocyte stimulating factors. Dogs are more susceptible to these myelotoxic effects than cats. The effects of estrogens on the bone marrow occur in several stages. Initially a leukocytosis occurs. At the same time an increase in platelet numbers, followed by severe thrombocytopenia is observed. The leukocytosis is followed by leukopenia, which persists for a period of approximately three weeks. Leukopenia and thrombocytopenia are seen within two weeks of bone marrow injury. This is followed

by a decrease in erythrocyte production. Anemia is often delayed in onset, because of the longer life span of erythrocytes (120 days, compared to 4 to 8 hours for leukocytes and 5 to 7 days for platelets) (Kearns and Ewing, 2006; Sontas et al., 2009; De Bosschere and Deprest, 2010). Recovery, in cases of acute injury and especially in chronic cases, may take weeks to months after the removal of the causative agent. In cases of chronic exposure to estrogens, damage is often irreversible and leads to a replacement of the red bone marrow by fat or fibrous tissue (75-100%). This results into irreversible neutropenia, thrombocytopenia and moderate to severe anemia (Kearns and Ewing, 2006; Sontas et al., 2009; De Bosschere and Deprest, 2010). Estrogen-induced myelotoxicity may be caused by exogenous estrogens or endogenous estrogens produced by ovarian or testicular neoplasms (Sontas et al., 2009) and should be a major differential for pancytopenia in cryptorchid dogs or dogs suspected of testicular tumors.

Therefore, a complete blood examination is usually performed in canine cases suspected of testicular neoplasia. Especially hematology is important because of the possible myelotoxic effects when the tumor is secreting estrogens (Kearns and Ewing, 2006; Sontas et al., 2009; De Bosschere and Deprest, 2010). In cases with leukopenia, pancytopenia and/or fever, urinalysis is also indicated. It may reveal the presence of pyuria, bacteriuria, proteinuria and hematuria, due to urinary tract infections (Dhaliwal et al., 1999; Lawrence and Saba, 2013). Myelotoxicosis occurs in 15% of the individuals with Sertoli cell tumors (Sanpera et al., 2002). Most of the time a moderate non-regener-

ative anemia, leukopenia, neutropenia and/or severe thrombocytopenia are detected (Sanpera et al., 2002; Plavec et al., 2007; Warland et al., 2011; Quartuccio et al., 2012). In cases of testicular neoplasia presenting with signs of myelotoxicosis, it is therefore useful to determine the concentration of circulating estrogens (estradiol 17 β), which is often elevated. Many, but not all, of these dogs also show external symptoms of feminization (Sanpera et al., 2002; Plavec et al., 2007; Warland et al., 2011; Quartuccio et al., 2012). De Bosschere and Deprest (2010) reported a case of a nine-year-old Beauceron with estrogen-induced pancytopenia without obvious clinical signs related to feminization. On the other hand, feminization symptoms may be subtle, and hence may remain unnoticed. Unexpectedly, in a study of Mischke et al. (2002), not all dogs with clinical symptoms of feminization had increased concentrations of estradiol. Other authors also report wide variation in estradiol concentrations in dogs with Sertoli cell tumors, varying from 10-150 pg/mL with a reference value below 15 pg/mL (Feldman and Nelson, 2004). Therefore, not only an absolute elevation of the estrogen levels, but also an imbalance of estrogen versus testosterone concentrations is thought to be important. The amount of estrogen production is directly proportional to the size and location of the tumor. Large tumors are often located in the abdomen and are associated with a higher production of estrogen (Mischke et al., 2002).

Furthermore, medical imaging should be carried out in patients suspected of testicular tumors, in order to determine the location and extension of the neoplastic process. Thoracic radiographs can be useful in detecting metastases in the lungs or thoracic lymph nodes, although this is seen infrequently. Abdominal radiographs can reveal the neoplastic testicle as an abdominal soft tissue mass effect. Abdominal radiographs were not performed in this case, because ultrasonography was available and is considered to be more sensitive in the detection of neoplastic cryptorchid testicles and abdominal metastases. Sometimes, fine needle aspirates are taken from the abdominal mass, mostly to confirm its neoplastic origin (Dhaliwal et al., 1999; Barrand and Scudamore, 2001; Sanpera et al., 2002; Kim and Kim, 2005; De Bosschere and Deprest, 2010; Hong et al., 2011; Warland et al., 2011; Lawrence and Saba, 2013).

Bone marrow aspirates can be very helpful to support the diagnosis of pancytopenia and especially to estimate the prognosis. In cases of estrogen toxicity, necrotic and inflammatory lesions can be seen in the bone marrow, which may develop into a condition of hypocellularity in chronic cases. In particular, hypocellularity in combination with replacement of the red bone marrow by fat or fibrous tissue indicates a poor prognosis (Sontas et al., 2009). Bone marrow aspiration and biopsy were discussed with the owners of this dog, but they preferred to evaluate the effect of the surgery without examining the bone marrow.

Castration is the treatment of choice in dogs with testicular tumors, regardless of the presence of paraneoplastic syndromes. The removed testicles should be sent for histopathological examination to allow detection and typing of any small early testicular neoplasm. In some cases, the contralateral testicle is atrophied and shows signs of severe fibrosis on histopathological examination (Dhaliwal et al., 1999; Kim and Kim, 2005; Bosschere and Deprest, 2010; Carreira et al., 2012). In the present case, the contralateral descendent testicle was indeed atrophied, but also contained neoplastic tissue.

In cases with concurrent pancytopenia, additional treatment aims to correct the hematologic abnormalities, provide protection against secondary infections and stimulate the remaining bone marrow elements. Fluid therapy, full blood or packed red blood cell transfusions and broadspectrum bactericidal antibiotics can be used as supportive treatment. Because repeated transfusions are sometimes needed, it is advised to use donors of the same blood type and perform crossmatches before every blood transfusion (Sanpera et al., 2002; Sontas et al., 2009). In human medicine, androgens may have beneficial effects on bone marrow recovery in aplastic anemia of different causes (Sontas et al., 2009). Nandroloneacetate, an anabolic steroid, was successfully used in a canine case of estrogen-induced myelotoxicity (De Bosschere and Deprest, 2010). Four months after starting the treatment, hematological variables almost completely normalized. Lithium carbonate is another treatment option that stimulates the proliferation of pluripotent stem cells by an unknown action. It has already been used with success for cyclic hemato-poiesis and in some cases of estrogen-induced myelotoxicity in dogs (Maddux and Shaw, 1983; Hall, 1992; Weiss, 2003; Sontas et al., 2009). On the other hand, beneficial effects with lithium carbonate did not occur in a case reported by Sanpera et al. (2002). During treatment, serum or plasma lithium levels and renal values should be monitored to see if the drug reaches optimum therapeutic levels (dog: 0.5-1.8 mmol/L) and because of possible nephrotoxic effects (Sontas et al., 2009). In human medicine, the treatment of choice is bone marrow transplantation. Bone marrow transplantations are not frequently performed in practice because of the difficulties to find a compatible donor (Weiss, 2003). In the present case, the dog died unexpectedly shortly after discharge from the clinic, and prior to the start of additional drugs to stimulate bone marrow recovery. A possible explanation for the initial improvement of the dog, before discharge, could be the beneficial effect of the blood transfusion that was carried out during hospitalization.

Chemotherapy has been rarely used in dogs as adjuvant treatment of testicular tumors because castration is usually a curative treatment and these tumors usually have a low metastatic potential. Methotrexate, vinblastine and cyclophosphamide can be useful in

cases with metastases and also cisplatin has proven to be efficient in two out of three treated dogs (Dahliwal et al., 1999).

In general, the prognosis for hyperestrogenism is considered to be unfavorable if severe hematologic abnormalities are present (Dahliwal et al., 1999; Feldman and Nelson, 2004; Lawrence and Saba, 2013). In case of a positive response, initial signs of bone marrow regeneration usually occur within three to six weeks after castration and supportive therapy (Feldman and Nelson, 2004). To the authors' knowledge, there are no large studies describing a median survival time and the percentage of dogs that show hematologic recovery.

It is especially important for practitioners to prevent possible life-threatening paraneoplastic syndromes by advising elective castration, both of the undescendent and the descendent testicle, in every case of cryptorchidism. Besides the prevention of paraneoplastic syndromes, castration of cryptorchid dogs is also recommended to prevent further spread of this condition as it is a hereditary trait within several dog breeds (Feldman and Nelson, 2004).

CONCLUSION

Testicular tumors are commonly seen in cryptorchid dogs and can be associated with a possibly life-threatening estrogen-induced pancytopenia. It is crucial to remove both testes in cases of cryptorchidism in order to prevent tumor formation, potential paraneoplastic syndromes and because of genetic implications. Early recognition of feminization may potentially prevent life-threatening irreversible estrogen-induced bone marrow hypoplasia.

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Uit het verleden

DE PEST IN ATHENE (430 - 426 vChr.)

Deze vorm van ziekte, die geen woorden kunnen beschrijven, overviel eenieder met een groter geweld dan de menselijke natuur kon verdragen en bleek onder meer van gewone ziekten vooral in volgend opzicht te verschillen: de vogels en dieren die lijken eten, hoewel er vele doden onbegraaven lagen, kwamen er niet op af, of als zij ervan hadden gegeten, stierven ze. Een bewijs hiervan was de opvallende afwezigheid van zulke vogels, die noch bij de lijken noch elders te zien waren. Maar de honden die met mensen samen leefden, gaven meer gelegenheid om de uitwerking van de ziekte waar te nemen.

Velen stierven door verwaarlozing, anderen ondanks de beste verpleging. Nog anderen overleefden.

Meer nog hadden medelijden met de zieken en de stervenden, zij die van de ziekte hersteld waren. Zij wisten wat het was en voelden zich veilig, want voor de tweede maal greep de ziekte niemand aan, althans niet met dodelijke afloop. Zij werden gelukkig en in hun vreugde van het moment koesterden zij de lichtvaardige hoop in de toekomst nooit meer aan een andere ziekte te zullen sterven.

Fragmenten uit Thucydides, *Historiae*, II

Ondanks de uitvoerige en accurate beschrijving van de ramp die zowel stad als platteland trof - niet toevallig - tijdens een oorlog, is men er lange tijd niet in geslaagd de aard van de ziekte met enige zekerheid vast te stellen. In 1995 echter bleek uit de studie van DNA uit een massagraf in het centrum van Athene dat de ziekte niet verwekt was door de klassieke oorzaken van pest zoals *Yersinia pestis*, Anthrax of pokken, maar door *Salmonella enterica* serovar Typhi, de verwekker van tyfus. De door Thucydides beschreven symptomen komen hiermee overeen, al kenden tyfusedemieën in latere tijden een veel trager verloop.

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