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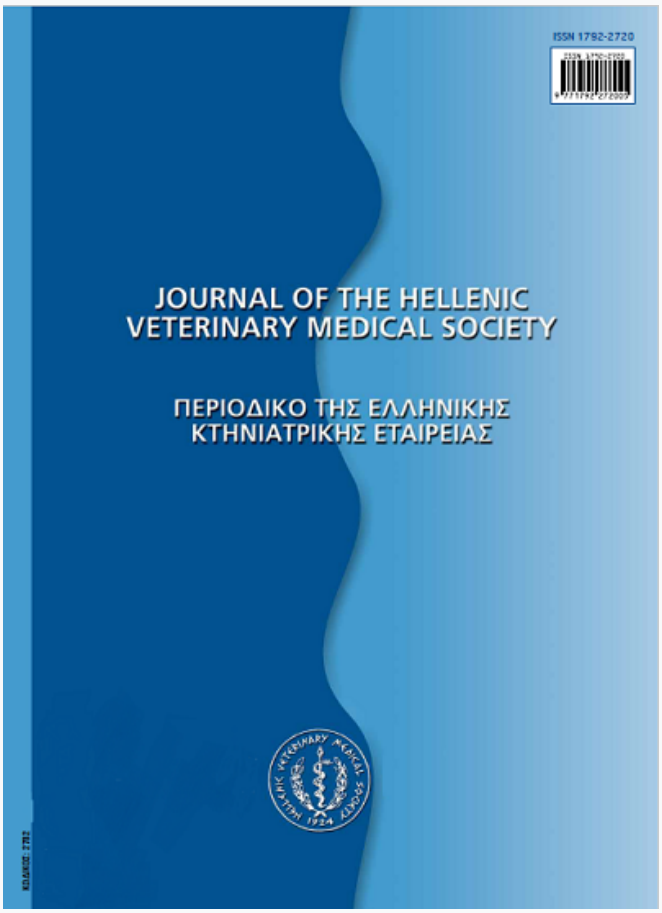


# Cutaneous transmissible venereal tumor with internal metastases in two dogs

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Cases report
Κλινικά περιστατικά

# Cutaneous transmissible venereal tumor with internal metastases in two dogs

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# Δερματικό γενικευμένο αφροδίσιο μεταδοτικό νεόπλασμα σε δύο σκύλους

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**ABSTRACT.** Two intact male dogs, a 6-year-old Siberian husky (case one) and an 18-year-old Old English sheepdog-cross (case two), were admitted to the Companion Animal Clinic, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki (AUTh), with a single or multiple cutaneous masses, respectively. Fine needle aspiration (FNA) smears obtained from the masses revealed the typical cytological features of transmissible venereal tumor (TVT) in both instances, while *Leishmania infantum* infection was diagnosed in the second case. In both dogs, distant metastases within the spleen and liver were diagnosed by ultrasonography-assisted FNA cytology, laparotomy-facilitated histopathology and computed tomography (case one) or post-mortem cytology and histopathology (case two). Vincristine sulphate (two weekly sessions) followed by doxorubicin chemotherapy (five 3-week sessions) failed to achieve clinical remission in case one, while the dog in case two was euthanized without any therapeutic effort. This study describes the clinical, imaging, cytologic and pathologic findings of two dogs with primary cutaneous TVT metastasized internally. Chemotherapy resistance, rarely recorded in TVT, was documented in one of them, whereas concurrent *Leishmania* infection in the other dog might have provoked the dissemination of TVT presumably due to the *Leishmania*-associated immunosuppression.

***Keywords:*** dog, transmissible venereal tumor, chemotherapy resistance, leishmaniosis

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**ΠΕΡΙΛΗΨΗ.** Ένας σκύλος ηλικίας 6 ετών, αρσενικός ακέραιος, φυλής Siberian husky (περιστατικό 1) και ένας σκύλος 18 ετών, αρσενικός ακέραιος, μιγάς φυλής Old English sheepdog (περιστατικό 2), προσκομίστηκαν στην Κλινική Ζώων Συντροφιάς της Κτηνιατρικής Σχολής του Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης (Α.Π.Θ.) για τη διερεύνηση δερματικού όγκου στην αριστερή επιγονάτια πτυχή καθώς και διαλειπόντων εμέτων και επίσταξης κατά τις τελευταίες 10 ημέρες (περιστατικό 1) και για τη διερεύνηση πολλαπλών δερματικών μαζών (περιστατικό 2). Στην κλινική εξέταση διαπιστώθηκε οργανομεγαλία στην πρόσθια κοιλία και στους δύο σκύλους, ενώ, σε κανένα δεν παρατηρήθηκαν αλλοιώσεις στα γεννητικά όργανα. Η διάγνωση βασίστηκε στην κυτταρολογική εξέταση επιχρισμάτων μετά από παρακέντηση με λεπτή βελόνα των δερματικών μαζών. Η κυτταρολογική εικόνα χαρακτηριζόταν και στα δύο περιστατικά, από την παρουσία ενός ομοιόμορφου πληθυσμού στρόγγυλων κυττάρων με μεγάλους στρόγγυλους πυρήνες, αδρή χρωματίνη, συχνά εμφανείς πυρηνίσκους, πολυάριθμες μιτώσεις και κυτταρόπλασμα με πολυάριθμα μεγάλα κενοτόπια, που διατάσσονταν με τη μορφή αλυσίδας συνήθως στην περιφέρεια του κυτταροπλάσματος, ευρήματα διαγνωστικά για το αφροδίσιο μεταδοτικό νεόπλασμα. Στο περιστατικό 2, βρέθηκαν επιπλέον αμαστιγοφόρες *Leishmania infantum*. Και στα δύο περιστατικά διαπιστώθηκαν μεταστάσεις στο ήπαρ και το σπλήνα με τη διενέργεια αξονικής τομογραφίας και λαπαροτομής (περιστατικό 1) ή νεκροτομής (περιστατικό 2) και την επακόλουθη κυτταρολογική και ιστοπαθολογική εξέταση (περιστατικά 1 και 2) (Εργαστήριο Παθολογικής Ανατομικής, Κτηνιατρική Σχολή, Α.Π.Θ). Στο περιστατικό 1, πραγματοποιήθηκαν 2 συνεδρίες βινκριστίνης (0.6 mg/m$^2$, ενδοφλέβια, κάθε 7 ημέρες) και 5 συνεδρίες δοξορουβικίνης (30 mg/m$^2$, ενδοφλέβια, κάθε 21 ημέρες) σε συνδυασμό με σπληνεκτομή, χωρίς να επιτευχθεί κλινική ύφεση, με τελική έκβαση το θάνατο του ζώου, 10 περίπου μήνες μετά την αρχική προσκόμισή του. Στο περιστατικό 2 έγινε ευθανασία χωρίς καμία θεραπευτική προσπάθεια. Στην εργασία αυτή, περιγράφονται τα κλινικά, απεικονιστικά, κυτταρολογικά και ιστοπαθολογικά ευρήματα δύο περιστατικών αφροδισίου μεταδοτικού νεοπλάσματος με πρωτογενή εντόπιση στο δέρμα, χωρίς αλλοιώσεις στα εξωτερικά γεννητικά όργανα και με πολυεστιακές μεταστάσεις στο ήπαρ και στο σπλήνα. Παράλληλα, σχολιάζονται τα ασυνήθιστα ευρήματα της ανθεκτικότητας στη χημειοθεραπεία που διαπιστώθηκε στο ένα περιστατικό και ο πιθανός ρόλος της μόλυνσης από τη *Leishmania infantum* στην διασπορά του νεοπλάσματος στο άλλο περιστατικό.

***Λέξεις ευρετηρίασης:*** σκύλος, αφροδίσιο μεταδοτικό νεόπλασμα, ανθεκτικότητα στη χημειοθεραπεία, λεϊσμανίωση

## INTRODUCTION

In canine transmissible venereal tumor (TVT) the mode of transmission is by implantation of neoplastic cells through damaged skin and accessible mucosae (Rogers 1997, de Lorimier and Fan 2007). The exact origin of this neoplasm is still unknown, with some studies suggesting a histiocytic lineage and others identifying neoplastic cells overall as leukocytes (Albanese et al. 2002, Gatone et al. 2003, Gross et al. 2005, Levy et al. 2006). External genitalia is the most common site of TVT, mainly because of copulation-induced microtraumas (Rogers 1997, Das and Das 2000). However, several extragenital sites have been reported such as the skin, oral and nasal cavities, conjunctival mucosa and rectum, most likely due to certain social behavioral patterns of the dog (e.g. sniffing, licking, rubbing) (Rogers 1997, Boscos et al 1998). Dissemination (i.e. distant metastases) of TVT is fairly uncommon, with a frequency ranging from 0 to 17% in previous reports (Brown et al. 1980, Calvert et al. 1982, Rogers 1997, Rogers et al. 1998). In most of the affected dogs prognosis is good to excellent after vincristine chemotherapy, with a complete cure rate exceeding 90%, even in animals with distant metastases (Calvert et al 1982, Amber et al. 1990, Rogers 1997, Rogers et al. 1998).

The present report describes two unusual cases of primary cutaneous TVT, with multiple internal metastases. The first case was highly resistant to sequential chemotherapy with vincristine and doxorubicin, while the second experienced concurrent *Leishmania infantum* infection.

## CASE HISTORY

### Case one

A 6-year-old, intact male, Siberian husky was admitted to the Companion Animal Clinic, Faculty of Veterinary Medicine, AUTh with a history of intermittent vomiting and epistaxis of ten-day duration. Physical examination revealed the presence of a firm, painless, cutaneous tumor measuring 3×4 cm, at the left lateral thigh. Other findings included mild prescapular lymphadenomegaly, unilateral abdominal cryptorchidism, umbilical hernia and palpable organomegaly at the cranial abdomen. Thorough examination of the external genitalia revealed no gross lesions. Complete blood count (IDEXX Laser Cyte Hematology Analyser, IDEXX Laboratories Inc, USA) disclosed mild erythrocytosis (57.1%, reference intervals: 37-55%) and mature neutrophilia (14,290/μl, reference intervals: 3,000-12,000/μl). Serum biochemistry (Vitalab Flexor E Clinical Chemistry Analyser, Vital Scientific, The Netherlands) revealed hyperproteinemia (9.8g/dl, reference intervals: 5.5-8g/dl), and elevated

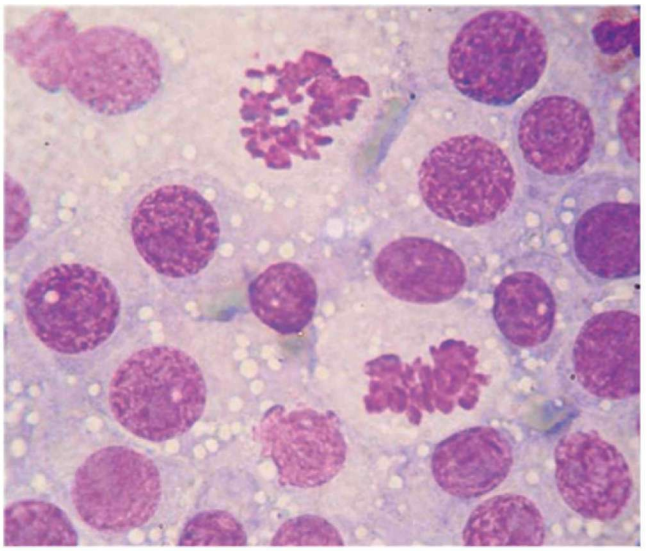

**Figure 1:** Case 1. Fine needle aspiration cytology from the cutaneous mass, demonstrating round cells with several and variably-sized clear vacuoles and two mitotic figures. Giemsa, 100x objective.

alkaline phosphatase (2,275U/L, reference intervals: 32-149U/L) and gamma-glutamyl transferase (35U/L, reference intervals: 1-3U/L) activities. Serological testing for *Leishmania infantum* (Canine Leishmania Antibody Test Kit, IDEXX Laboratories Inc, USA) and *Dirofilaria immitis* (Canine Heartworm Antigen Test Kit, IDEXX Laboratories Inc, USA) was negative, but a low-to-moderate antibody titer for *Ehrlichia canis* was detected by applying a semiquantitative ELISA assay (Immunocomb, Biogal, Israel). Thoracic radiography was unremarkable but abdominal radiography disclosed moderate hepatomegaly and splenomegaly. Fine needle aspiration (FNA) cytology of the cutaneous mass revealed a monomorphic population of round cells, characterized by large nuclei, coarse chromatin pattern and usually prominent nucleoli, numerous mitotic figures, and a bluish cytoplasm dotted with variably-sized and well-demarcated clear vacuoles (Figure 1). These findings were indicative of cutaneous TVT. Bone marrow and prescapular lymph node aspiration cytology did not show neoplastic cells or *L. infantum* amastigotes. At that time, the owner declined abdominal ultrasonography, or rhinoscopy to investigate the etiology of epistaxis. Chemotherapy with vincristine sulphate (Oncovin, Pharmaserve Lilly, Greece) was initiated, at the dose of 0.6 mg/m², intravenously, at weekly intervals, but was discontinued after the second session due to poor tumor remission. During these two weeks the dog experienced intermittent vomiting and mild anorexia. Abdominal ultrasonography revealed hepatomegaly and splenomegaly along with multiple, well demarcated hypoechoic lesions throughout the hepatic and splenic parenchyma (Figure 2A). Microscopic examination of ultrasound-guided FNA slides obtained from both organs, showed similar cytological features, suggesting distant metastases of the tumor. Computed tomography (CT) of the abdominal cavity confirmed that the lesions were localized only in the spleen and liver. The later appeared hypoattenuated compared to the adjacent normal parenchyma with no enhancement after intravenous contrast medium administration (Figure 2B). Chemotherapy with doxorubicin (Adriblastina, Pharmacia & Upjohn, Greece) at 30 mg/

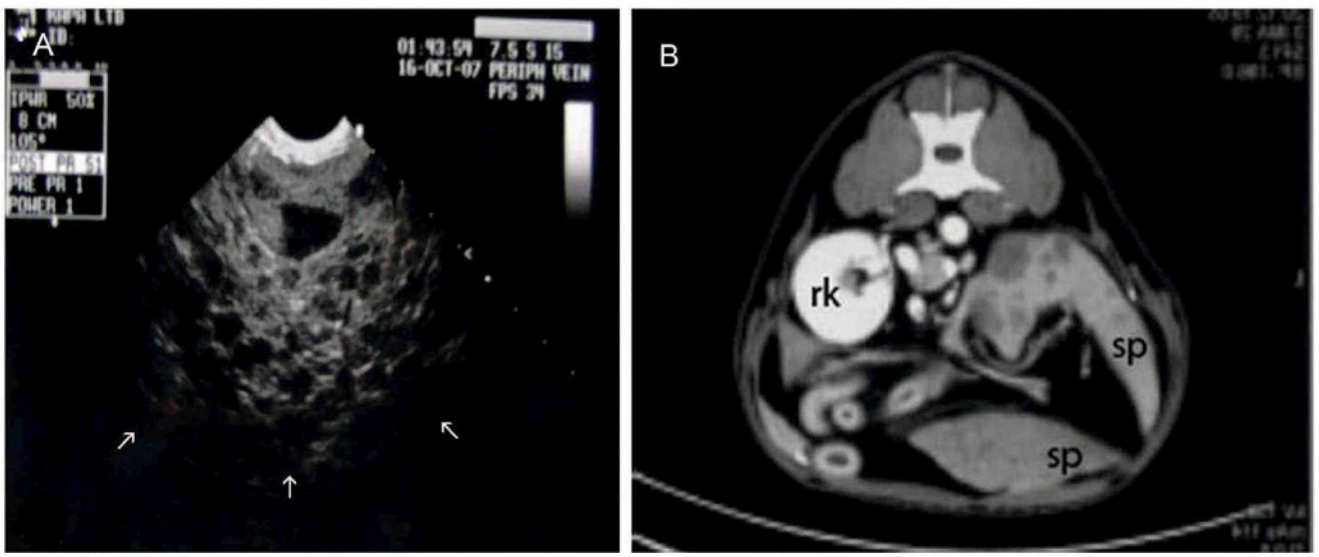


**Figure 2:** Case 1. (A) B-mode image of the hepatic parenchyma, depicting multiple well defined hypoechoic lesions scattered all over. (The arrows demonstrate the hepatic margin) (B) Transverse computed tomographic image at the level of the right kidney (rk) after intravenous contrast medium administration. There are multiple well defined not enhanced lesions throughout the parenchyma of an enlarged spleen (sp).

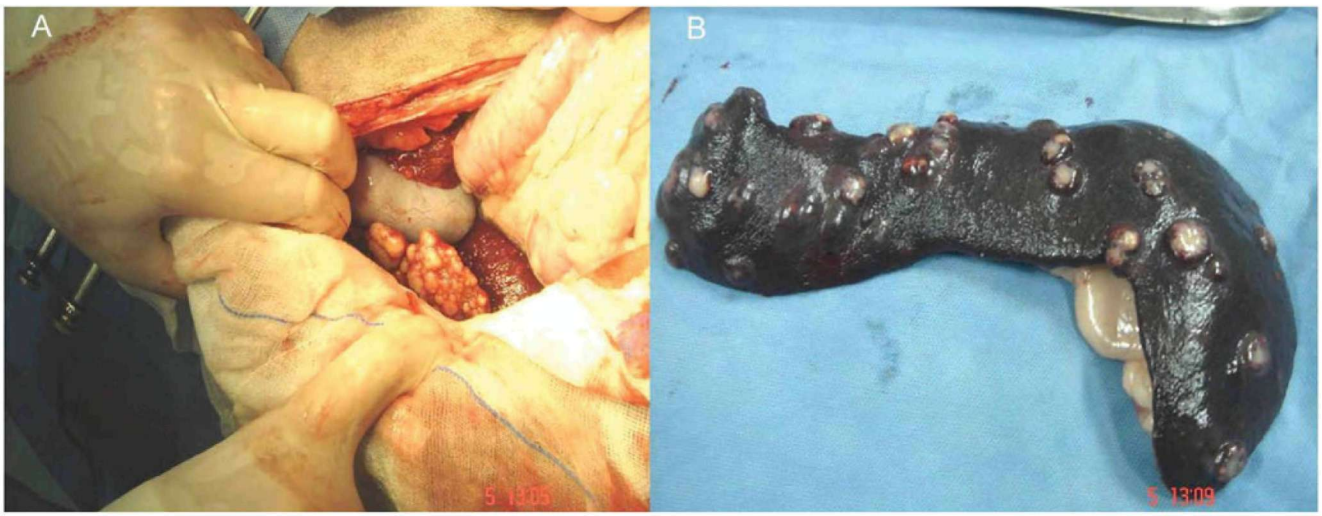


**Figure 3:** Case 1. Notice the numerous nodules appearing on the liver (A) and spleen (B) during the laparotomy.

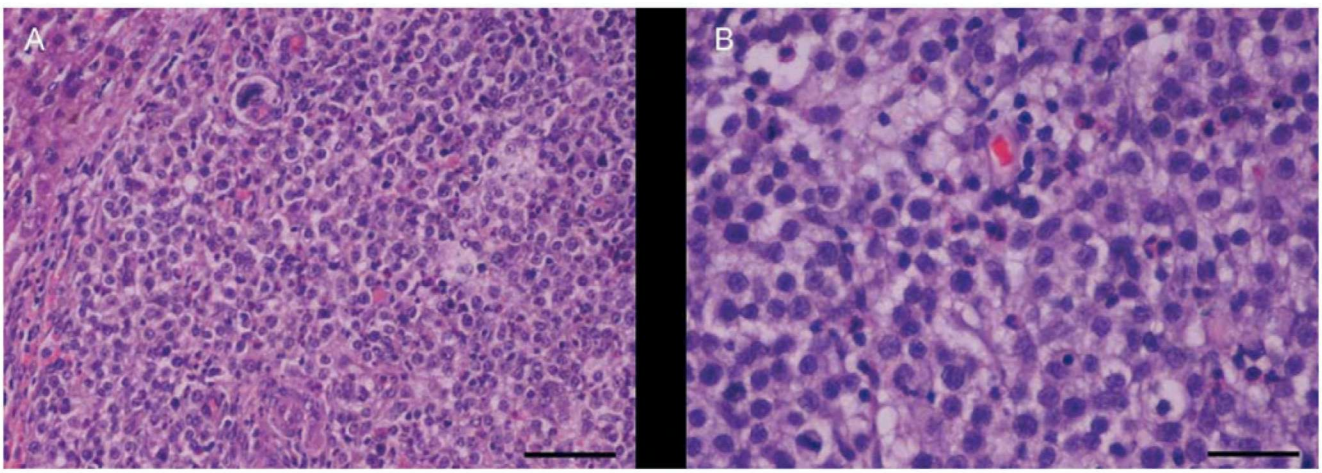


**Figure 4:** Case 1. Histopathology of the hepatic (A) and splenic (B) transmissible venereal tumor nodules, showing sheets of large pleomorphic cells, bearing variable number of intracytoplasmic vacuoles, that are more visible in the spleen (B); mitotic figures are quite plentiful (B). H&E, bar=300μm (A) and bar=150μm (B).

$m^2$, intravenously, every three weeks, was initiated, but after two sessions and apart from a moderate regression of the cutaneous tumor, liver and spleen pathology remained essentially unchanged, according to an ultrasonographic follow-up. Surgical debulking with splenectomy was decided at that time, before proceeding to the next series of doxorubicin chemotherapy. Upon laparotomy numerous nodules were visualized on the liver and spleen (Figure 3A and B), the histopathology of which confirmed the TVT metastasis. The histologic appearance of the hepatic nodules consisted of several round, mostly well-defined neoplastic foci that had obliterated the normal hepatic architecture and were clearly separated by fibrous septae. The foci consisted of solid sheets of voluminous round cells, bearing large round nuclei, prominent nucleoli, coarsely aggregated chromatin and discrete cytoplasmic vacuoles (Figure 4A). The neoplastic population was highly pleomorphic in terms of cellular and nuclear size and showed a high mitotic rate [≥3 mitoses per high power field (HPF)]. Splenic nodule histopathology was similar to that of the liver, apart from the higher mitotic rate (3-10 mitoses/HPF), the greater number of cells with cytoplasmic vacuoles and the larger cellular size (Figure 4B). Following a total of five doxorubicin sessions and despite the resolution of erythrocytosis and hyperglobulinemia, the clinical condition of the dog deteriorated, along with the appearance of new cutaneous TVT lesions. The animal eventually died ten months post admission, but permission for necropsy was not granted by the owner.

## Case two

A 18-year-old, intact male, Old English sheepdog-

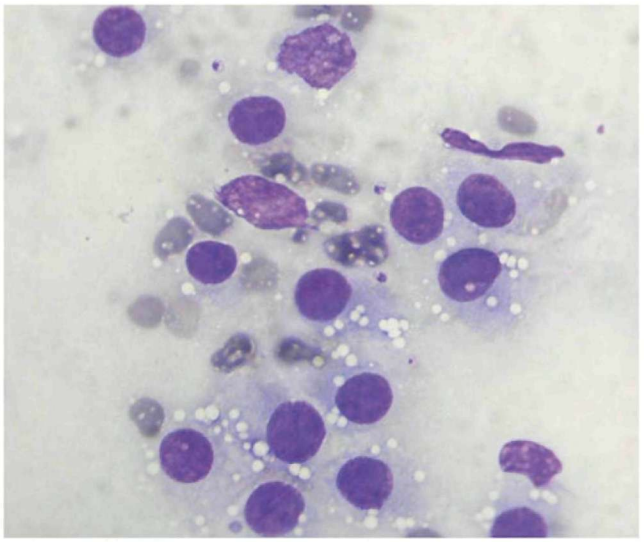

**Figure 5:** Case 2. Fine needle aspiration cytology from the cutaneous mass, demonstrating *Leishmania* amastigotes amidst neoplastic round cells. Giemsa, 100x objective.

cross was admitted because of multiple skin masses, appeared during the last 12 months. On physical examination there were several firm, painless subcutaneous masses and one ulcerated cutaneous nodule (located on the neck), mild peripheral lymphadenomegaly and palpable hepatosplenomegaly; no lesions were found on the external genitalia. FNA cytology of the skin masses was typical of TVT, along with numerous *Leishmania* amastigotes, noticed extracellularly (Figure 5). Prescapular lymph node cytology revealed several parasites but no neoplastic cells. The owner declined any further investigation or treatment and opted to have the dog euthanized. Post mortem examination revealed four subcutaneous, round-to-oval exuberant tumors. They were localized on the neck, right lateral abdomen and left thoracic wall, measuring 4 cm to 8.5 cm in diameter. Multiple and a single metastatic nodules were visualized on the enlarged spleen and liver, respectively (Figure 6). FNA and impression smear cytology from the internal organs confirmed the concurrence of TVT and *Leishmania* infection. The relevant cutaneous, splenic and hepatic histopathology was quite similar to that of case one, apart from the inconspicuous cytoplasmic vacuolation.

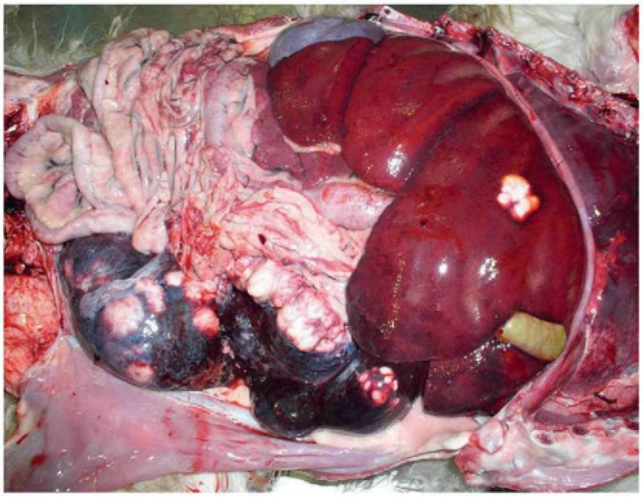

**Figure 6:** Case 2, post mortem. Multiple metastatic nodules appearing on the spleen and a single nodule on the liver.

## DISCUSSION

Canine TVT has a worldwide distribution with higher incidence in areas with large populations of free-roaming dogs and suboptimal breeding practices (Rogers 1997, Das and Das 2000, Papazoglou et al. 2001, Boscos and Ververidis 2004, Levy et al. 2006). There is no clear age, gender or breed predisposition, but large breeds of dogs, as those of the current two cases, are affected more frequently (Rogers 1997, Das and Das 2000, de Lorimier and Fan 2007).

Extragenital TVT is generally uncommon, accounting for less than 10% of the admitted cases, with the cutaneous, oral and nasal localizations prevailing (Brown et al. 1980, Calvert et al. 1982, Thrall 1982, Rogers 1997, Rogers et al. 1998, Papazoglou et al. 2001, Levy et al. 2006, Mylonakis et al. 2008). Neck, dorsum, flank and limbs are the most common sites of cutaneous TVT, as it was the case of these two dogs (Das and Das 2000, Marcos et al. 2006). Occasionally, a diffuse nodular pattern may be noticed over almost the entire thoracic and abdominal areas (Albanese et al. 2006). In voluminous skin neoplasms, ulceration and necrosis may also occur, as it was witnessed in case two (Rogers 1997, Das and Das 2000). The frequency of distant metastases, seen mainly in young or immunosuppressed animals does not exceed 6% and 17% in the experimental and natural TVT, respectively (Rogers et al. 1998, Das and Das 2000, Albanese et al. 2002, Albanese et al. 2006, Park et al. 2006). However, these figures may be higher, since in the majority of the reported cases there has been no use of advanced imaging techniques to look for possible subclinical visceral TVT metastases (Calvert et al. 1982, Amber et al. 1990, Rogers et al. 1998, Nak et al. 2005, Scarpelli et al. 2010). The metastatic pattern in both of the current cases was very similar (spleen and liver involvement). Other metastatic sites such as the oral cavity, kidneys, peritoneum, central nerv ous system, eyes, lungs and the mediastinum have been reported

(Rogers 1997, Boscos et al. 1998, Ferreira et al. 2000, Albanese et al. 2006, Park et al. 2006). In case one, the cause of immunosuppression remains unknown. The seropositivity to *E. canis* indicates prior exposure to the agent, but does not endorse active infection, especially taking into account the incompatible hematologic findings including erythrocytosis, neutrophilia and normal thrombocyte counts (Mylonakis et al. 2008). Polymerase chain reaction might have been useful in this respect (Mylonakis et al. 2008). In addition, there has been no evidence to support the notion that the non-myelosuppressive type of *E. canis* infection in the dog causes immunosuppression (Hess et al. 2006). On the other hand, the concurrent leishmaniosis may have contributed to TVT dissemination in the second dog, because of the suppression of cellular immune response that it may cause, or, alternatively, the potential tumor-induced immune system dysregulation may have provoked the development of clinical leishmaniosis in an infected asymptomatic dog (Albanese et al. 2002, Gatone et al. 2003, Levy et al. 2006).

The epistaxis observed in the first dog could be the result of primary or metastatic nasal TVT, since it responded well to chemotherapy(Papazoglou et al. 2001), in contrast to the skin tumor. The intermittent vomiting in the same case was most likely due to massive spleen and liver infiltration. The quite uncommon erythrocytosis, also witnessed in this dog, could be the result of erythropoietin production by the multiple neoplastic masses, as it was resolved by the end of doxorubicin chemotherapy (Rogers 1997, Bergman 2007). The elevated activity of the hepatic enzymes and hypeglobulinemia, also observed in case one, probably reflected the hepatic infiltration and the chronic antigenic stimulation by the neoplastic process, respectively.

In TVT, the diagnosis is mainly based on the cytologic examination of FNA smears obtained from primary and/or metastatic masses. The high mitotic index and the numerous, well demarcated intracytoplasmic vacuoles allow for a reliable differentiation from other more common round cell skin tumors (e.g. lymphomas, histiocytomas and mast cell tumors) (de Lorimier and Fan 2007). Histopathology usually provides confirmation of the cytologic diagnosis, although its diagnostic sensitivity may occasionally be suboptimal due to inconspicuous or absent cytoplasmic vacuolation, as it was the case in the second dog (Gross et al. 2005). Advanced diagnostic imaging may be helpful in localizing either primary or metastatic lesions in unusual anatomic sites (Ferreira et al. 2000). In case one, CT reliably demonstrated the abdominal dissemination of TVT, in concordance with the laparotomy findings. However, the hypoechoic and hypoattenuating TVT nodules in the liver and spleen appear similar to those associated with other conditions, such as benign hyperplasia, nodular regeneration, lymphoma and histiocytic neoplasms (Cruz et al. 2004).

Vincristine chemotherapy has been very effective in TVT, with cure rates exceeding 90%, even in the disseminated disease (Calvert et al. 1982, Amber et al. 1990, Singh et al. 1996, Rogers et al. 1998, Nak et al. 2005). Although in most of the dogs subjected to this kind of chemotherapy there has been a substantial regression of the tumor within the first two weeks, case one did not respond, thus urging the medical staff to switch to doxorubicin, as the most suitable alternative (Brown et al. 1980, Calvert et al. 1982, Rogers et al. 1998, Nak et al. 2005, de Lorimier and Fan 2007). Nevertheless, doxorubicin is not invariably effective in vincristine-resistant TVT cases, as only 50% of these dogs eventually respond (Calvert et al. 1982, Rogers et al. 1998, Nak et al. 2005). Unfortunately the first dog did not belong to the latter subset, because the five doxorubicin sessions were unrewarding, even with the aid of surgical debulking. There is limited information regarding the factors influencing the time to clinical remission following chemotherapy or the overall outcome (complete remission or not). In a recent study with TVT cases undergone vincristine therapy, the large tumor size, increased age of the dog and therapy initiation during the hot and rainy months of the year delayed the clinical remission (Scarpelli et al. 2010).

## CONCLUSION

Extragenital TVT is a relatively uncommon clinical occurrence, with cutaneous and nasal localizations representing the bulk of the reported cases. Internal metastases are rarely described and may herald a poor prognosis. Despite the chemoresponsive nature of TVT, occasional cases may demonstrate resistance to multiple chemotherapeutic agents. Further studies are warranted to unearth the factors responsible for this kind of resistance.

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