### Intraocular transmissible venereal tumors in dogs: a retrospective review of 21 cases

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Intraocular transmissible venereal tumors in dogs: a retrospective review of 21 cases

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Abstract

Twenty-nine canine intraocular transmissible venereal tumors (TVT) tissue samples from 21 dogs diagnosed between 2008–2014 were reviewed retrospectively. The following clinical data were compared: patient signalment, onset of clinical signs, ophthalmic signs, location of intraocular lesion, duration of unilateral intraocular TVT to bilateral intraocular TVT during the two-year follow-up period, and treatment. Thirty-eight percent (8/21) of the dogs with intraocular TVT eventually had bilateral intraocular TVT within two years. Seventy-five percent (6/8) of the dogs with bilateral intraocular TVT had initially presented with a unilateral lesion. Two dogs presented with intraocular TVT had no history of genital and extragenital TVT. Chemotherapy did not lead to complete remission of intraocular TVT in contrast to that for genital and extragenital TVT. Enucleation was performed for all affected eyes. The spread of genital/extragenital TVT to unilateral or bilateral intraocular TVT should be considered and monitored for at least 24 months or longer.

Keywords: dog, eye, intraocular, transmissible venereal tumor

1. Introduction

Transmissible venereal tumors (TVT) commonly affects the genitalia. TVT is a histolytic tumor of the external genitalia and is transmitted during mating. It represents one third of known transmissible cancers in mammals. This tumor can occur at any age and affects all dog breeds and no sex predilection. TVT is benign tumor and is shown to regress in dogs with good body condition (Santos et al., 2008). In dogs with reduced immune response such as stressed, young, old, immunosuppressed or in general poor health, the tumor tends to grow aggressively and metastasize (Albanese, Salerni, Giodarno,
& Marconato, 2006; Boscos, Ververidis, Tondis, Stamou, & Samartzi, 1998; Ferreira et al., 2000; Mukaratirwa & Gruys, 2003). TVT cells are transmitted by contact of genital mucous membranes (Papazoglou, Koutinas, Plevraki, & Tontis, 2001), and extragenital TVT can occur in nasal or oral cavity via licking or sniffing the genital TVT (Siddle & Kaufman, 2014). Metastatic TVT spreads via hematogenous (Albanese et al., 2006; Ferreira et al., 2000) and lymphatic routes (Miller, Albert, & Boosinger, 1990; Rodrigues, Alessi, & Laus, 2001). The metastatic rate of TVT is 1.5–6% (Das & Das, 2000; Dass & Sahay, 1989; Pigatto, Hunning, Bercht, & de Albuquerque, 2011; Rodrigues et al., 2001). Ocular involvement may be primary extragenital tumors via mucous membrane contact (Abbott, 1966; Komnenou, Thomas, Kyriazis, Poutahidis, & Papazoglou, 2015; Milo & Snead, 2014; Pigatto et al., 2011) or represents as metastatic tumors (Almeida et al., 2003; Boscos et al., 1998; Ferreira et al., 2000; Komnenou et al., 2015; Pereira, Silva, Martins, Ferreira, & Brooks, 2000; Rodrigues et al., 2001). Intraocular TVT tends to be more often presented as metastatic tumors than primary tumors (Das & Das, 2000; Ferreira et al., 2000; Pereira et al., 2000; Rodrigues et al., 2001). Metastasis of TVT to the eye has been reported at the conjunctiva (Boscos et al., 1998), nictitating membrane (Almeida et al., 2003), orbit (Dass & Sahay, 1989) and intraocular tissue (Ferreira et al., 2000; Miller et al., 1990; Pereira et al., 2000; Rodrigues et al., 2001). The common presenting clinical signs of intraocular TVT are uveitis and elevated intraocular pressure (Pereira et al., 2000).

The objective of this study was to review the signalment, clinical signs, the timing link with other site and the second eye being affected, and the results of chemotherapeutic protocols.

2. Materials and Methods

Clinical data of 21 dogs with 29 intraocular TVT tissue samples were retrieved from the out-patient clinic and ophthalmology clinic of Kasetsart University Veterinary
Teaching Hospital, Bangkok, Thailand during June 2008–October 2014. Clinical data included the sex, breed, age, onset of ophthalmic signs of intraocular TVT noticed by the owners after genital or extragenital TVT diagnosis, ophthalmic signs examined with slit-lamp biomicroscopy and tonometry, duration of unilateral intraocular TVT to bilateral intraocular TVT over a two-year follow-up period, treatment, and affected intraocular structure from histopathological examination. In the case of unilateral intraocular TVT, the second eye was monitored during the two-year follow-up period.

Diagnosis of intraocular TVT was made by cytological (5 eyes) and histopathological examination (24 eyes). Cytology was done in case of visual in the first time. Sector iridectomy was performed in one eye for histopathology due to its unidentified cytology. Twenty-nine eyes were enucleated and twenty-four eyeballs were submitted for pathological examination. The eyeballs were fixed in 10% (w/v) formalin, embedded in paraﬃn, sectioned at 4 µm and then stained with haematoxylin and eosin (H&E). Histopathological diagnosis of TVT based on the histopathological criteria (Agnew & MacLachlan, 2017; Komnenou et al., 2015). Intraocular TVT was characterized by an unencapsulated mass of round cells with large round nuclei, prominent single to bi-nucleoli and abundant cytoplasm. Cells were moderately anisocytosis and contained a high mitotic index.

Immunohistochemistry was performed on two eyes from two dogs which had no history of genital or extragenital TVT. The specimens were sectioned at 4 µm, placed on positively charged slides for labeling with S-100 protein (4C4.9, Cell Marque™, California, USA), melanosome (HMB45, Dako Denmark A/S, Glostrup, Denmark), vimentin (V9, Cell Marque™, California, USA), cytokeratin (AE1/AE3, Novocastra™, Newcastle upon Tyne, UK), melan A (A103, Novocastra™, Newcastle upon Tyne, UK), CD3 (Dako Denmark A/S, Glostrup, Denmark) and Pax5 (1EW, Novocastra™, Newcastle
Upon Tyne, UK). Immunohistochemical examination for S-100 protein, melanosome, vimentin and cytokeratin was performed on the auto-immunohistochemistry stainer, Leica Microsystems Bond maX System (Leica Microsystems, Bannockburn, IL) according to the manufacturer's recommendation by Institute of pathology, Department of Medical Services Ministry of Public Health, Bangkok, Thailand. Immunohistochemistry for Melan A, CD3 and Pax5 was performed using the standard protocol (Pereira et al., 2000). Briefly, all sections were performed by an antigen retrieval method in citrate buffer (pH 6.0) at 720 w in a microwave oven for 16 minutes before immunohistochemical staining. The specimens were incubated with primary antibody for 60 minutes in a humidified chamber at 37°C. The antibodies were made visible with an indirect immunoperoxidase method. The secondary HRP-conjugated anti-rabbit antibody (Dako EnvisionTM+/HRP kits) was applied. Diaminobenzidine chromogen was added to the specimens. The sections were counterstained with Mayer’s hematoxylin.

Chemotherapy with vincristine sulfate (0.7 mg/m² IV weekly) for 4-6 weeks was administered for intraocular TVT in four dogs, with doxorubicin (30 mg/m² IV three weeks interval) for 2-3 cycle in two intraocular dogs, and with vincristine followed by vinblastine (2 mg/kg IV two weeks interval) combined with methotrexate (0.1 mg/kg PO every other day) in one intraocular dog. Enucleation without chemotherapy was performed due to severe uveitis and glaucoma in fourteen dogs. The follow up for the second eye was done until two years post-operatively.

3. Results

Of the 21 dogs with intraocular TVT, 19 were male with only two females. Mean age were 5.52 ± 2.23 years (range 2–10 years). Sixteen were mixed breed and the others were Golden retrievers (2), Shih Tzu (1), Chihuahua (1) and Poodle (1). Only two dogs presented with bilateral intraocular TVT. Seven dogs had a previous history of genital
TVT, two dogs had a previous history of genital TVT concurrent with extragenital TVT and one dog had a history of extragenital TVT at subcutaneous tissue at the dorsal thorax.

Three dogs had concurrent intraocular TVT with genital TVT. One dog had intraocular TVT with extragenital TVT and one had intraocular TVT with genital and extragenital TVT at the time of presentation. Two dogs did not have any history of TVT. At the two-year follow-up period, unilateral intraocular TVT was diagnosed in 13 dogs (six in the right eye and seven in the left eye) and bilateral intraocular TVT was diagnosed in eight dogs (Table 1).

The most common presenting signs of intraocular TVT were conjunctivitis (96.55%; 28/29), vision loss (89.66%; 26/29), corneal edema (86.21%; 25/29), abnormal mass within the eye (75.86%; 22/29), aqueous flare (75.86%; 22/29), secondary glaucoma (62.07%; 18/29), buphthalmos (55.17%; 16/29), hyphema (48.28%; 14/29) (Fig. 1) and ocular perforation (6.90%; 2/29).

Cytological results showed numerous round cells. These cells have round, concentric nuclei with 1-2 prominent nucleoli. Chromatin was coarse and sometime mitosed. Cytoplasm was abundant with some refractile vacuoles. Histopathological findings of intraocular masses after enucleation revealed typical TVT with unencapsulated mass of loosely packed round cells separated by delicate fibrovascular stroma. Cells have hyperchromatic, round to oval nuclei, coarse chromatin, and prominent nuclei as found in cytology. Cells were moderately anisocytotic. Mitotic figures were frequently seen (Fig. 3a). Intraocular TVT were found in the iris and ciliary body in 19 eyes and involved the iris, ciliary body and choroid in 5 eyes (Fig. 2). Immunohistochemical study of an ocular mass in two dogs with no history of genital or extragenital TVT revealed tumor cells were immunopositive for vimentin (Fig. 3b) and negative for the S-100 protein, melanosome, melan A, cytokeratin, CD3 and Pax5 (Figs. 3c–h).
The mean duration of intraocular TVT signs after presentation of genital or extragenital TVT of 14 dogs observed by the owner was 6.5 ± 8.4 months (range 0–24 months), while the mean duration of intraocular TVT spreading from one eye to the other of 8 dogs was 5.6 ± 8.0 months (range 0–24 months).

Weekly single agent (vincristine) chemotherapy was used for treatment of genital or extragenital TVT in nine dogs (cases no. 1, 2, 3, 7, 10, 11, 14, 15, 16), and led to complete remission after 4–8 weeks of treatment in eight dogs. One dog (case no. 1) did not respond to the treatment, and the genital and subcutaneous skin form of TVT spread to the lymph nodes. This dog was subsequently administered vinblastine with doxorubicin (Calvert, Leifer, & MacEwen, 1982), the TVT masses at the subcutaneous tissue and lymph nodes were partial remission. Surgical removal of a subcutaneous mass and inguinal lymph nodes together with biopsy of inguinal lymph nodes was performed. One dog (case no. 4) declined genital TVT chemotherapy treatment. Surgical mass removal at back and dorsal thorax was done in one dog (case no. 8) without chemotherapy. The information regarding treatment of genital or extragenital TVT could not be retrieved in eight dogs (cases no. 5, 6, 13, 17, 18, 19, 20, 21). Two dogs (cases no. 9, 12) did not have history of genital or extragenital TVT. Chemotherapy was subsequently performed in seven dogs with intraocular TVT. Four dogs (cases no. 2, 3, 5 and 14) received vincristine (Pigatto et al., 2011; Ucar, 2016) (0.7 mg/m² IV weekly), two dogs (cases no. 1 and 7) received doxorubicin (Calvert et al., 1982) (30 mg/m² IV three weeks interval) and one dog (case no. 11) received vincristine followed by vinblastine (Singh, Rana, Sood, Pangawkar, & Gupta, 1996) (0.1 mg/kg IV two weeks interval) combined with methotrexate (Boscos, 1988) (0.1 mg/kg PO every other day). Enucleation without chemotherapy was performed in 14 dogs due to severe intraocular damage.
Chemotherapy was unsuccessful in treating the intraocular masses in all the dogs. Initially, the masses showed partial remission and the ocular signs improved, but then the tumors recurred and progressed. Hence, enucleation was recommended due to the uncontrolled severe uveitis and secondary glaucoma.

4. Discussion

In this study, intraocular TVT presented more frequently in male than female dogs, consistent with a previous report (Boscos, 1988; Boscos et al., 1998; Komnenou et al., 2015; Papazoglou et al., 2001; Srivastava, Singh, Srivastava, Sharama, & Sinha, 2013). In addition, the previous report of metastatic cases is mostly observed in adult male dogs (Boscos, 1988; Pandey, Chandpuria, Bhargava, & Tiwari, 1989). This result contrasted with a report which stated that the incidence of TVT was more common in female than male dogs (Santiago-Flores, Jaro, Recuenco, Reyes, & Amparo, 2012; Singh et al., 1996). That can possibly be explained by the male behavior of mating with several females (Das & Das, 2000; Komnenou et al., 2015). A recent report suggested that no gender difference in canine TVT (Strakova & Murchison, 2014). However, intraocular involvement has not been reported.

Canine TVT is commonly reported in dogs 2-5 years of age (Pigatto et al., 2011; Das & Das, 2000). That is consistent with the average age of intraocular TVT in this report. Increased sexual activity with young age is a possible explanation of this age of incidence (Pigatto et al., 2011; Santiago-Flores et al., 2012).

Mixed breed was the most common type of dog in this state, which was consistent with some previous reports (Calvert et al., 1982; Komnenou et al., 2015; Papazoglou et al., 2001; Rogers, Walker, & Dillon, 1998; Srivastava et al., 2013) and in contrast with one previous report (Das & Das, 2000). This might simply reflect that mixed breeds form the major proportion of the dog population in Thailand, rather than their greater susceptibility.
Uveitis and glaucoma were the most common presenting signs, similar to that previously reported (Pereira et al., 2000).

In the two-year follow up period, the duration of development of intraocular TVT after genital or extragenital TVT ranged from 0 to 24 months. The longest time observed for the spread from one to the other in this study was 24 months. Therefore, at least a 24-month if not longer follow-up period is recommended. In general, sector iridectomy in an early-detected iridal tumor may be beneficial for saving the eye (Diters, Dubielzig, Aguirre, & Acland, 1983; Gelatt, Johnson, & Peiffer, 1979), but it seemed to be an ineffective treatment for intraocular TVT because of the high risk of recurrence (Dass & Sahay, 1989; Komnenou et al., 2015; Ucar, 2016). This is consistent with our finding in dog no. 11. Close monitoring of ocular abnormalities after an initial TVT diagnosis might be useful for early detection but ultimately unlikely to change the outcome.

Intraocular TVT was mostly found at the anterior or posterior uvea because they are highly vascularized and is where metastatic cells enter the eye (Ferreira et al., 2000). Local invasion from masses next to the eye was rare because of the tough fibrous coat being the barrier (Gould, 2003). It was surprising that intraocular TVT possibly occurred even without pre-existing genital or other extragenital TVT as cases no. 9 and 12. Those two dogs that had only one owner since young had no history of genital and extragenital TVT. Extraginal TVT in the absence of pre-existing genital involvement was typically the result of primary auto or hetero-implantation (Milo & Snead, 2014). The mechanism of intraocular TVT without pre-existing genital or extragenital TVT is still elusive.

Biopsy was the most reliable method for definitive diagnosis of TVT (Das & Das, 2000; Nak, Nak, Cangul, & Tuna, 2005). However, diagnosis of intraocular TVT from two dogs with no history of preexisting TVT were confirmed by negative immunohistochemical staining to S-100, melanosome, melan A, cytokeratin, CD3 and...
Pax5, in addition to the positive staining for vimentin (Mozos, Mendez, Gomez-Villamandos, Martin de las Mulas, & Perez, 1996; Pereira et al., 2000). Their expression was used for differential diagnosis excluded lymphomas, histiocytic tumors, amelanotic melanomas, poorly differentiated carcinomas, and poorly differentiated mast cell tumors (Mascarenhas et al., 2014; Mozos et al., 1996; Pereira et al., 2000). Vimentin is a specific marker of mesenchymal derivation or differentiation (Leader, Collins, Patel, & Henry, 1987; Mascarenhas et al., 2014; Mukaratirwa & Gruys, 2003) and stains positive in TVT, fibrosarcomas, melanomas, hemangiosarcomas, mastocytomas, leiomyosarcomas and liposarcoma (Pereira et al., 2000). However, S-100 was used to differentiate TVT from neurogenic sarcoma, melanoma, hemangiosarcomas, liposarcomas and leiomyosarcomas (Ferreira et al., 2000; Pereira et al., 2000), while melanosome and melan A were used to rule out melanomas (Pereira et al., 2000). Cytokeratin was used to differentiate TVT from poorly differentiated carcinomas, such as squamous cell carcinomas and apocrine adenocarcinoma/carcinoma (Ferreira et al., 2000; Mozos et al., 1996; Pereira et al., 2000), while CD3, Pax5 and vimentin were used to differentiate TVT from lymphomas (Ferreira et al., 2000; Pereira et al., 2000). Previous immunohistochemical studies for canine TVT were lysozyme, ACM1 and alpha-1-antitrypsin (ATT) (Mozos et al., 1996; Mukaratirwa and Gruys, 2003), to which specific histiocytic cell origin and canine TVT. Immunoreactivity of lysozyme was variable, 0% (Mascarenhas et al., 2014), 40% (Mozos et al., 1996) and 100% (Marchal, Chabanne, Kaplanski, Rigal, & Magnol, 1997) whereas ACM1 was 79% (Marchal et al., 1997) and ATT was 56% respectively (Mozos et al., 1996). The differential diagnosis between TVT and histiocytomas should be based on clinical and histiopathologic characteristics (Mozos et al., 1996; Mukaratirwa & Gruys, 2003) because there is no significant difference between the immunophenotype of histiocytomas and TVT. These results confirmed that intraocular TVT should also be
considered in dogs with no history of genital or extragenital TVT. According to previous reports, metastases can occur in dogs that had no primary genital or extragenital TVT, if the primary lesion had completely regressed before examination (Boscos et al., 1998; Das & Das, 2000; Mozos et al., 1996).

Standard treatment for genital TVT was chemotherapy with vincristine. The remission ranged from 82–100% (Amber, Henderson, Adeyanju, & Gyang, 1990; Calvert et al., 1982). Complete remission of TVT of the adnexa, such as conjunctiva and nictitating membrane, tended to be achieved after chemotherapy with vincristine (Almeida et al., 2003; Boscos et al., 1998; Komnenou et al., 2015; Milo & Snead, 2014; Pigatto et al., 2011). In contrast, intraocular TVT was not responsive to treatment with vincristine (Ferreira et al., 2000; Miller et al., 1990; Pereira et al., 2000). Doxorubicin was usually effective for genital or extragenital TVT remission (Calvert et al., 1982; Nak et al., 2005). However, vincristine or doxorubicin failed to provide complete intraocular TVT remission in this study. A combination of vinblastine and methotrexate, which had a variable response on genital TVT, was also ineffective for complete intraocular TVT remission. Regardless of chemotherapy and response, intraocular TVT usually causes severe uveitis and secondary glaucoma resulting in enucleation (Boscos, 1988; Pereira et al., 2000; Rodrigues et al., 2001; Willis & Wilkie, 2001).

5. Conclusions

This report presents characteristics of intraocular TVT including signalment, common clinical signs, duration of genital TVT or extragenital TVT spreading to intraocular TVT and duration of intraocular TVT spreading from one to the other eye. In addition, intraocular TVT with no previous history of genital or extragenital TVT may be present and should be considered. All eyes with intraocular TVT required enucleation.
Unfortunately effective chemotherapy or treatment techniques for intraocular TVT are not yet available.

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Figure 1. Clinical presentation of intraocular TVT of the right eye, showing the hyphema, hypopyon, posterior synechia and iris mass at 5–7 o’clock (arrow).

Figure 2. (a) The iris shows massive infiltration of discrete cells that displayed hyperchromatic nuclei, prominent nucleoli and abundant cytoplasm. Vascular congestion and multifocal necrosis are also seen. Posterior chamber accumulated infiltrating inflammatory cells, necrotic debris and red blood cells. (b) Iris and ciliary body are massively infiltrated by neoplastic cells. (c) An unencapsulated mass of neoplastic discrete cells over the choroid causing retinal separation and distortion. (I: Iris, PC: Posterior chamber, L: Lens, CB: Ciliary body, AC: Anterior chamber, Ch: Choroid, Sc: Sclera) (H&E, 4x)
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Figure 3. (a) Histopathological findings of a poorly circumscribed unencapsulated mass of neoplastic discrete cells display hypercellularity and moderately anisocytosis. Cells contain hyperchromatic nuclei, prominent single to sometimes binucleoli and abundant cytoplasm. Mitotic index are high. H&E, positive immunoreactivity for (b) vimentin, and negative immunoreactivity for (c) S-100 protein, (d) melanosome, (e) melan A, (f) cytokeratin, (g) CD3 and (h) Pax5. (Bar = 20 µm).
Table 1: Signalment and duration of intraocular transmissible venereal tumor (TVT) after presenting with external genitalia or extragenital TVT

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n/a = not available because of diagnosis by cytology

-* = Intraocular TVT was present only in one eye