Sex disparity in oronasal presentations of canine transmissible venereal tumour

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Abstract

Background

The canine transmissible venereal tumour (CTVT) is a contagious cancer spread by the direct transfer of living cancer cells. CTVT usually spreads during mating, manifesting as genital tumours. Oronasal CTVT is also occasionally observed, however, and presumably arises through oronasal contact with genital CTVT tumours during sniffing and licking.

Methods

Given that sniffing and licking transmission behaviours may differ between sexes, we investigated if oronasal CTVT shows sex disparity.

Results

Twenty-seven of 32 (84%) primary oronasal tumours in a CTVT tumour database occurred in males. In addition, 53 of 65 (82%) primary oronasal CTVT tumours reported in the published literature involved male hosts. These findings suggest that male dogs are at four to five times greater risk of developing primary oronasal CTVT than females. This disparity may be due to sex differences in licking and sniffing activity, perhaps also influenced by sex differences in CTVT tumour accessibility for these behaviours.

Conclusion

Although oronasal CTVT is rare, it should be considered as a possible diagnosis for oronasal tumours, particularly in male dogs.

Introduction

The canine transmissible venereal tumour (CTVT) is a contagious cancer affecting dogs. CTVT is a clonal lineage, thus the living cancer cells themselves act as infectious agents and are physically passed between dogs. CTVT originated in a single dog living several thousand years ago (1-5), and has since spread through the canine population worldwide (6). The disease is prevalent in countries with free-roaming dog populations, but also occurs elsewhere in dogs imported from endemic areas (6, 7).

Mating is the most common route of CTVT transmission, and CTVT usually manifests clinically as tumours associated with the external genitalia in both male and female dogs (8). However, extra-genital body sites, including skin, eyes, nasal areas, mouth, rectum and internal organs can also be affected (6, 9-21). In these instances, if genital involvement co-occurs, the most likely CTVT seeding routes would appear to be either internal metastatic dissemination, or self-transmission (8, 20). The latter could occur, for example, when a dog licks its own genital tumour, or makes oronasal contact with its genital tumour while in a curled up sleeping position. However, in rare cases, primary extra-genital CTVT tumours in the absence of genital involvement are observed, which are most likely a result of non-copulatory CTVT transmission. This could occur during activities such as licking, sniffing, scratching or parturition (9, 11-15, 22-24).

One form of extra-genital CTVT which often poses a diagnostic challenge is primary oronasal CTVT (8, 22). Oronasal CTVT is observed rarely (6, 21, 22, 25), although to our knowledge no studies have systematically addressed its prevalence. Oronasal CTVT tumours present as soft-tissue masses within the nasal or oral cavities, leading to clinical signs such as

sneezing, snoring, mucopurulent nasal discharge or bleeding, and facial deformation (23, 26, 27) (Fig. 1). Imaging can in some cases reveal paranasal bone destruction (23, 26).

CTVT affects both male and female dogs and, although some studies have reported a higher prevalence in females (22, 28, 29), overall, no consistent sex disparity in CTVT has been reported (6, 30, 31). Variation in prevalence of oronasal CTVT between the sexes has not been systematically examined, however, even though there is reason to suspect that there might be sex-linked variation in risk. In females, genital CTVTs commonly involve the vulva, and are thus more accessible for licking or sniffing than male genital CTVTs, which usually occur at the base of the penis and are enclosed within the prepuce. Further, male sensory exploration of female genitals by licking or sniffing may be more common than male same-sex or female activity. In this study, we investigated the hypothesis that primary oronasal CTVT occurs more commonly in male dogs than in female.

Materials and methods

This study was approved by the Department of Veterinary Medicine, University of Cambridge, Ethics and Welfare Committee (reference number CR174, 11 November, 2015). A database with 1916 records of dogs with confirmed or suspected CTVT tumours was used in this study. The CTVT tumour data were collected between 2009 and 2020 by more than one hundred participating veterinarians and other animal health professionals working in first opinion clinical practice, referral clinics or at mass spay/neuter clinics in 59 countries in all inhabited continents. CTVT tumours in the database were considered "suspected" if their diagnosis was based on clinical presentation and clinical history only; "confirmed" CTVT was diagnosed with histopathology, cytology, genetic analysis or a combination of the above (32-35). All extra-genital CTVT tumours were considered confirmed. Sex and primary infection

site data were available for all 1916 cases. CTVT tumours were classified as genital (defined as primary genital tumours with possible involvement of other sites), oronasal (defined as primary oronasal tumours with no genital involvement) and other extra-genital (defined as primary tumours affecting body sites other than the genital or oronasal areas, such as ocular, cutaneous and rectal tumours). Two primary oronasal CTVT tumours had co-occurring tumours involving non-genital body sites (in both cases, eyes).

A literature review was performed in February 2022 by searching for reports of nasal, oral or oronasal CTVT in the published literature using PubMed and Google Scholar databases. Articles were retained if they reported one or more cases of confirmed primary oronasal CTVT, specified that the relevant animal had no genital involvement, and reported the host dog's sex. Four primary oronasal CTVT tumours were reported to have co-occurring tumours involving non-genital body sites (eyes, 3 tumours; rectum, 1 tumour). The published literature included in the analysis is presented in Supplementary file 1.

Exact binomial tests performed in R (36) were used to compare the observed numbers of males and females with primary oronasal CTVT in the study database and in the published literature to the 1:1 ratio expected under the null hypothesis.

Results

In the study database of 1916 dogs with confirmed or suspected CTVT tumours, 1865 had genital involvement. Among the 51 dogs diagnosed with CTVT without genital involvement, 32 had oronasal CTVT, and the remaining 19 had CTVT tumours affecting eyes, skin, rectum, urethra, or inguinal lymph nodes. This corresponds to a 1.7% prevalence of primary oronasal CTVT within this CTVT population (Table 1).

To test our hypothesis, that male dogs show a higher prevalence of primary oronasal CTVT than female dogs, we examined the sex of dogs hosting primary oronasal CTVT. Twenty-seven male and 5 female dogs with primary oronasal CTVT were recorded in the database. Assuming that these animals were drawn from an unbiased source population, this finding provides compelling evidence to discount the null hypothesis, that primary oronasal CTVT is equally distributed between the sexes (Table 2) (male proportion = 0.84, 95% confidence interval 0.67–0.95; $P = 0.0001$, exact binomial test).

A similar sex disparity in primary oronasal CTVT presentation was observed in the published literature. Fifty-three of the 65 cases of primary oronasal CTVT reported in the literature involved male dogs (male proportion = 0.82, 95% confidence interval 0.7–0.9; $P = 2.79 \times 10^{-7}$, exact binomial test with the null hypothesis that males and females are equally affected by primary oronasal CTVT) (Table 2, Supplementary file 1).

Discussion

These data suggest that male dogs are at four to five times greater risk of primary oronasal CTVT than female dogs (Table 2). However, this conclusion relies on the assumption that there was no sex bias in the selection of oronasal CTVT-affected dogs for inclusion in the CTVT database, or for inclusion in oronasal CTVT reports in the published literature.

The CTVT database used in this study was compiled from information submitted by more than one hundred participating veterinarians and animal health professionals working in 59 countries. Over variable time-periods between 2009 and 2020, these participants collected data about dogs with CTVT under their care. Several participants collected data while working

in mass spay/neuter campaign settings. Such efforts often prioritise sterilisation of female dogs, and, likely as a result of this, the database accessions are, as a whole, biased towards females (1245 females (65%), 671 males (35%) in the database of 1916 CTVT-affected dogs). This female-bias was still observed, although was less pronounced, in the overall CTVT data provided by participants who contributed one or more primary oronasal CTVT accession to the database (281 CTVT-affected dogs, 166 females (59%), 115 males (41%)). We cannot determine if the selection bias that affected the reporting of genital CTVT sex also affected reporting of primary oronasal CTVT sex. It is possible, for instance, that dogs with primary oronasal CTVT came to the attention of participating veterinarians via different routes (e.g. owners directly seeking veterinary care) compared with dogs with genital CTVT (e.g. incidental finding during spay surgery). However, if the female-biased reporting of genital CTVT found in the database applies equally to primary oronasal CTVT, and assuming that there were no biases that caused participants to over-report oronasal CTVT in males, then the true underlying sex disparity in primary oronasal CTVT might be even more pronounced than the four to five-fold increased male risk that we observed.

The finding that primary oronasal CTVT is reported approximately four times more often in male than female dogs in the published literature provides further evidence supporting the notion that male dogs are at greater risk of this form of CTVT. Although it cannot be excluded, we find no reason to believe that authors of published case reviews would be biased towards reporting oronasal CTVT in males. Overall, we believe that the best explanation for the observed disparity in oronasal CTVT prevalence in male and female dogs is an underlying difference in risk of contracting the disease.

The oronasal form of CTVT is probably usually acquired by licking or sniffing genital CTVT tumours or their secretions (8). Male dogs recognise oestrous females by sniffing the genitalia (37, 38), and male dogs sniff vaginal secretion odour more frequently than female dogs (39, 40). Further, female genital CTVT tumours tend to be more exposed and accessible for licking or sniffing than those of males, which are usually enclosed within the prepuce. Thus, the external location of female genital CTVT tumours, coupled with a likely male preference for licking or sniffing female genitalia, may contribute to increased risk of oronasal CTVT in males. It is not known whether CTVT itself is attractive to dogs; we can only speculate that its odour may mimic oestrus bleeding, which may attract males (2, 41).

Although male dogs appear to be at greater risk of oronasal CTVT, female dogs do also develop this form of CTVT. It follows that, presumably, females also engage in transmission behaviour including sniffing and licking genitalia of males or other females, but perhaps less frequently than males.

Fewer than two percent of CTVT cases contributed to the study database were of the primary oronasal form (Table 1). Although the inclusion bias in this database, discussed above, precludes estimation of the true proportion of CTVT cases that manifest oronasally, this finding is consistent with reports that primary oronasal CTVT is an unusual presentation of this disease (6, 21, 22, 25).

The rarity of oronasal CTVT in the population, despite the likelihood that opportunities for licking and sniffing transmission behaviour arise frequently, suggests that transmission of CTVT by sniffing or licking is an unlikely outcome. It is possible that sniffing or licking of CTVT tumours do not usually dislodge cancer cells or that, if dislodged, these cells are unlikely

to establish tumours in the recipient's oral or nasal cavities. CTVT cells have adapted for thousands of years to the genital environment, and oronasal sites are thus likely to be suboptimal for CTVT engraftment. Moreover, oronasal CTVT would appear to be an evolutionary dead end for this contagious cancer lineage, offering limited opportunities for further transmission.

Overall, we report a four to five-fold increased risk of primary oronasal CTVT presentation in male dogs compared with female dogs, highlighting the likely importance of behavioural differences between the sexes in CTVT disease risk when non-copulatory transmission routes are involved. CTVT should be considered as a possible diagnosis for oronasal tumours, especially in male dogs.

Acknowledgements

This work was supported by a grant from Wellcome (102942/Z/13/A). A.S. and A.B.-O. were supported by International Canine Health Postgraduate Student Inspiration Awards (made possible by a grant from Vernon and Shirley Hill) from the Kennel Club Charitable Trust to extend their research on canine transmissible venereal tumour. We acknowledge Martina Mayr & Animal Rescue Cambodia/Katherine Polak & FOUR PAWS and Ada Krupa for providing photos used in Fig. 1. We thank Kevin Gori, Maximilian R. Stammnitz and other members of the Transmissible Cancer Group for helpful discussions. We are very grateful to veterinary workers and organisations who contributed canine transmissible venereal tumour cases or other helpful information for this project, and especially acknowledge the support of: Umnt Arican, Cristóbal Briceño, María Verónica Brignone, Karina Ferreira de Castro, Natalia Ignatenko, Debra Kamstock, Ada Krupa, Mihran Lazyan, Adriana M. Lopez Quintana, Martina Mayr and Animal Rescue Cambodia, Mariana Bezerra Mascarenhas, Javier Ojeda Oyarzun,

Francisco Pedraza-Ordoñez, Katherine Polak and FOUR PAWS, John F. Reece and Help in Suffering, Maya Rybko, Cristian G. Torres and Alvaro S. Wehrle-Martinez.

Conflict of interest statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contributions

E.P.M. conceived, designed, and oversaw the study. A.S. contributed to study design and performed the overall study. A.B.-O. contributed to statistical analysis, data interpretation and literature review. J.W. contributed to data collection, data curation and CTVT diagnosis. A.S. and E.P.M. wrote the manuscript, with contributions from A.B.-O. All authors read and approved the final manuscript.

Data availability

The data that supports the findings of this study are available in the supplementary material of this article.

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Table 1

Summary of numbers of dogs with confirmed or suspected genital, oronasal and extra-genital (other) canine transmissible venereal tumours (CTVTs) in the study database (total number of CTVT cases = 1916). Dogs with more than one CTVT tumour are included in the "genital" category if one or more tumours involved the genitals, regardless of the body sites of additional tumours. "Extra-genital (other)" includes CTVT tumours affecting eyes, skin, rectum, urethra, or inguinal lymph nodes.

	Body site of CTVT tumour		
	Genital	Extra-genital	
		Oronasal	Extra-genital (other)
Number of dogs recorded in the study database	1865 (97.3%)	32 (1.7%)	19 (1%)

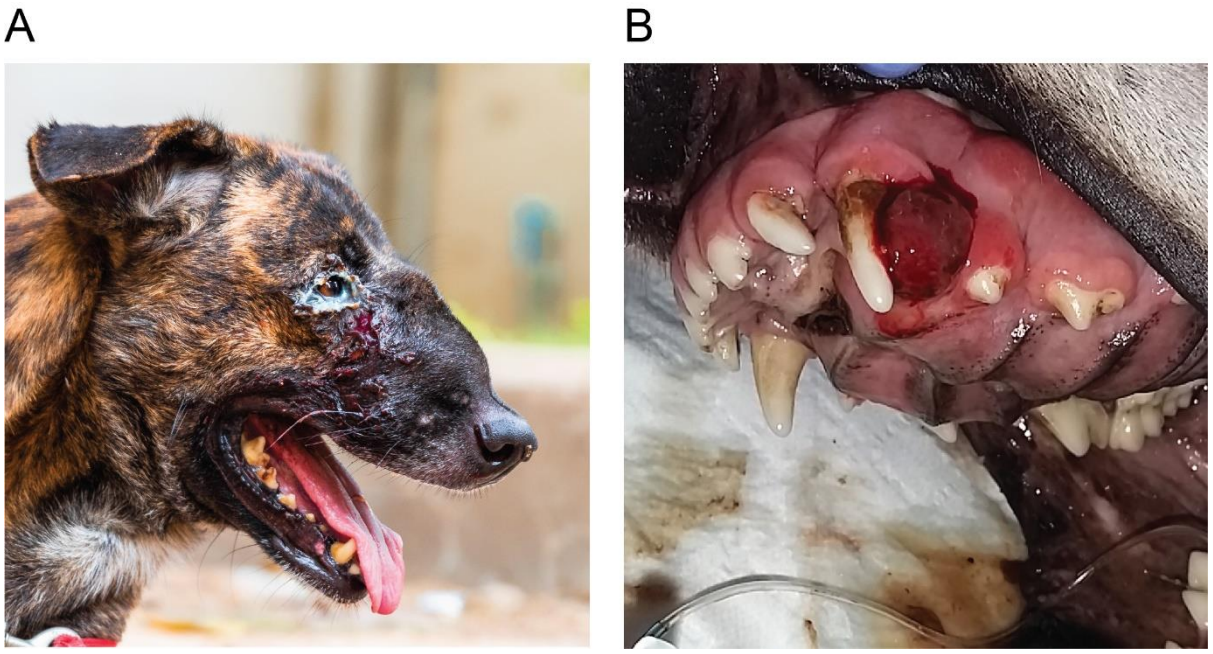
Table 2

Oronasal presentation of canine transmissible venereal tumour (CTVT) is more common in male dogs than in female dogs. Data from the study database and from the published literature are shown. Exact binomial tests were used to compare the observed numbers of males and females with primary oronasal CTVT to the 1:1 ratio expected under the null hypothesis of no difference between the sexes.

	Oronasal CTVT presentation			
	Male	Female	Male:female ratio	*P*-value
Study database	27 (84%)	5 (16%)	5.4:1	0.0001
Published literature	53 (82%)	12 (18%)	4.4:1	2.79×10^{-7}

Figure legends

Fig. 1: Oronasal presentation of canine transmissible venereal tumour (CTVT). CTVT affecting (A) nasal and (B) oral areas. Photographs provided by Martina Mayr (Animal Rescue Cambodia)/Katherine Polak (FOUR PAWS) and Ada Krupa.



Supplementary file legends

Supplementary file 1: Sex disparity in primary canine transmissible venereal tumour (CTVT) oronasal presentation in the published literature. Information about the first author, year published, publication title and number of male and female dogs with primary oronasal CTVT tumours is listed for each publication. Literature search was performed in February 2022. Reports that were noted in the literature but discarded from the analysis are listed, together with justification for excluding each report.