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Nosological and retrospective study of cases of extragenital transmissible venereal tumor in dogs

Estudo nosológico e retrospectivo de casos de tumor venéreo transmissível extragenital em cães

Estudio nosológico y retrospectivo de casos de tumor venéreo transmisible extragenital en perros

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Abstract

The transmissible venereal tumor (TVT) is well-documented and researched in dogs due to the unique characteristic of its transmissible cells. Despite of the vast scientific literature regarding genital TVT, the extragenital TVT is also present in many endemic countries, but the scientific descriptions about this disease came from isolated reports and case series. Thus, the objective of this study was to gather all the national and international information available of extragenital TVT in dogs and analyze it in the form of a systematic review, aiming understanding the countries with the highest incidence of cases, the relationship with the patients' review (race, sex and age), genital involvement, extragenital location, choice treatment and evolution of the disease. The results demonstrated 134 cases of the extragenital TVT with 214 extragenital lesions. The most of the studies came from Europe and South America. The mixed-bred dogs and males ranging from one to five years-old were the most commonly diagnosticated. The external organs were frequently affected and the ascendant tumor infiltration seemed was rare. The vincristine was the treatment of choice in almost all patients, having a complete remission in 79% of reported cases. In addition, it was observed that multiple lesions and chemoresistance can have a negative impact on the prognosis of this disease.

Keywords: Round cells; Metastasis; Oncology; TVT.

Resumo

O tumor venéreo transmissível (TVT) é bem documentado e pesquisado em cães devido à característica única de suas células transmissíveis. Apesar da vasta literatura científica a respeito do TVT genital, o TVT extragenital também está presente em muitos países endêmicos, mas as descrições científicas sobre a doença advém de relatos isolados e séries de casos. Assim, o objetivo deste estudo foi reunir todas as informações nacionais e internacionais disponíveis sobre o TVT extragenital em cães e analisá-las na forma de revisão sistemática, visando conhecer os países com maior incidência de casos, a relação com a resenha dos pacientes (raça, sexo e idade), envolvimento genital, localização extragenital, escolha do tratamento e evolução da doença. Os resultados demonstraram 134 casos de TVT

extragenital com 214 lesões extragenitais. A maioria dos estudos foram da Europa e América do Sul. Os cães mestiços e machos com idade entre um e cinco anos foram os mais comumente diagnosticados. Os órgãos externos foram frequentemente afetados e a infiltração tumoral ascendente foi rara. A vincristina foi o tratamento de escolha em quase todos os pacientes, apresentando remissão completa em 79% dos casos relatados. Além disso, observou-se que múltiplas lesões e quimiorresistência podem ter impacto negativo no prognóstico desta doença.

Palavras-chave: Células redondas; Metástase; Oncologia; TVT.

Resumen

El tumor venéreo transmisible (TVT) está bien documentado e investigado en perros debido a la característica única de sus células transmisibles. Apesar de la vasta literatura científica sobre TVT genital, TVT extragenital también está presente en muchos países endémicos, pero las descripciones científicas sobre la enfermedad provienen de informes aislados y series de casos. Así, el objetivo de este estudio fue recopilar toda la información nacional e internacional disponible sobre TVT extragenital en perros y analizarla en forma de revisión sistemática, con el objetivo de conocer los países con mayor incidencia de casos, la relación con la revisión de los pacientes (raza , sexo y edad), afectación genital, localización extragenital, elección del tratamiento y evolución de la enfermedad. Los resultados mostraron 134 casos de TVT extragenital con 214 lesiones extragenitales. La mayoría de los estudios se realizaron en Europa y América del Sur, siendo los perros cruzados y machos de entre uno y cinco años los que se diagnosticaron con mayor frecuencia. Los órganos externos se afectaban con frecuencia y la infiltración tumoral ascendente era rara. La vincristina fue el tratamiento de elección en casi todos los pacientes, con remisión completa en el 79% de los casos notificados. Además, se observó que múltiples lesiones y quimiorresistencia pueden tener un impacto negativo en el pronóstico de esta enfermedad.

Palabras clave: Células redondas; Metástasis; Oncología; TVT.

1. Introduction

The transmissible venereal tumor (TVT), also denominate of the Sticker tumor, canine condyloma, venereal granuloma, infectious sarcoma and venereal lymphosarcoma (Silva et al., 2007), is characterized by rounded-cell tumor and is one of the few capable of be

transmitted through transplantable cells (Tella et al., 2004; Huppes et al., 2014; Murchison, 2016).

Socializing habits among animals, especially of the dogs (sniffing), make them more predisposed to TVT, as well as the high number of stray and non-neutered animals (Tella et al., 2004; Huppes et al., 2014).

In dogs, the venereal regions most predominantly affected by TVT are the penis, vulva and vagina, however due to its transplantable properties, extragenital areas may be also involved through direct contact with the tumor cells. The principle extragenital locations reported in literature scientific are the skin, eyes and nasal cavity, being less commonly described in spleen, liver, lymph nodes and central nervous system. In this context, metastasis or ascension of genitalia to urogenital organs like urine bladder, uterus and ovary can also be present (Chiti & Amber, 1992; Ganguly et al., 2016).

The diagnostic method of choice for the TVT is cytology, being histopathological and immunohistochemical tests are less effective. Cytology shows round cell neoplasms, with central to eccentric nuclei and the presence of characteristic intracytoplasmic vacuoles (Huppes et al., 2014).

The occurrence of the TVT is worldwide with the exception of Antarctica. Countries located at the north regions of Europe and North America presents the lowest incidence rates, due to the small population of stray dogs (Ganguly et al., 2016).

Despite of the embraced literature about the genital TVT, information of the extragenital form is scarce and the published studies are based on isolated reports or case series studies. Like this, this study aimed to collect available information in the national and international literature about the extragenital TVT in dogs and organizes it as a systematic review, aiming understanding the countries with the highest incidence of cases, the relationship with the patients' review (breed, sex and age), genital involvement, extragenital location, choice treatment and evolution of the disease.

2. Methodology

Were selected published articles in national and international indexed journals from January 1980 until June 2017 using the following search terms: extragenital transmissible venereal tumor and extragenital TVT. The studies were located via search of the PUBMED, Google Academic and Science Direct, identifying articles written in Spanish, Portuguese and English.

The inclusion criteria for articles for the systematic review were based on the presence exclusive of extragenital TVT in dogs and not genital. Still, all manuscripts were carefully analyzed regarding their procedures used for diagnosing TVT and the definition by cytology or histopathology was mandatory. Besides that, were also recorded the country of origin of the publication, information about patient like breed, sex and age, concomitant presentation of genital TVT, localization of the extragenital TVT, treatment approach and evolution of the disease.

Extragenital sites of the TVT were classified in three groups: external organs (tumor secondary to direct contact with primary tumor - skin, eyes, oral and nasal cavity, mammary gland and perianal region); internal organs (metastasis in liver, spleen, lung, lymph node, central nervous system, peritoneum, and blood) and ascendant organs that possibly were affected secondary to invasion from the genitalia (bladder, ovary, uterus and kidneys).

After collecting the information, qualitative variables were described by percentages (Pereira et al., 2018).

3. Results

Were included 69 articles of the extragenital TVT, totalizing 134 dogs and 214 extragenital lesions. Ninety-nine articles were published since 2010 (74%), 27 from 2000 to 2009 (20%) and just eight cases (6%) were described before 2000.

Regarding geographical origin of the cases of the extragenital TVT, Europe presented the highest number (33.5%), followed by South America (32.8%), North America (14.7%), Asia (11.1%) and Africa (6.7%). The country with the highest number of reported cases was Greece with 35 animals, followed by Brazil with 30 cases and Grenada with 15 dogs.

Mixed-breed dogs were the most commonly affected, representing 55% of the whole population.

A higher number of males (52%) was observed when compared to female (40%) and 8% of dogs has no sex information.

Dogs most commonly affected for the extragenital TVT were between one to five years-old (50.7%), followed by dogs ranging from five to ten years-old (27.6%). Occurrence of extragenital TVT in dogs younger than 1-year-old (3.7%) and dogs older than ten years old (3%) was minimal. Information about age was not registered in 15% of cases.

Interestingly, most of the extragenital TVT cases lacked of genital involvement (68.6%).

Regarding extragenital sites, 70.2% of the cases presented a solitary extragenital lesion, 11.9% presented two extragenital lesions in different locations, 11.2% had three lesions in different locations and 6.7% presented with four or more lesions in different extragenital organs. Localization of TVT was found to be more common in external organs (68.2%) than internal (26.6%) and ascendant organs (5.2%).

The main locations of TVT in external organs were skin (19.6%), eyes (19.1%), nasal cavity (18.2%) and less frequently oral cavity (6%). When TVT was affecting external organs, no genital involvement was found in the majority of animals (72%).

Internal organs most commonly reported were spleen (6.6%), lymph nodes (5.7%), lungs (4.8%) and central nervous system (2.8%). Still, 71.4% of patients with TVT in the spleen presented hepatic infiltration of TVT. From the total of dogs with internal organ TVT, 39% had concomitant genital and external organ involvement; 39% presented exclusively external organ involvement and 22% presented exclusively genital involvement.

Extragenital TVT in organs considered of ascendant tumor invasion or genital metastasis was identified in just 11 dogs (8.2%), being the uterus (3), ovaries (3), kidneys (3) and bladder (2) the affected sites.

The chemotherapy, mostly based on vincristine - was the treatment of choice in 94 cases (70%), two dogs (1.4%) performed surgery as sole treatment and in the rest (28.6%) the treatment modality was not informed in the articles.

One-hundred-four cases had information regarding disease evolution. Of these, 82 dogs (79%) presented complete remission after chemotherapy and 3 (3%) presented recurrence after chemotherapy; 10 (9%) were euthanized after diagnosis, 6 (6%) died because of tumor related causes after chemotherapy treatment, and three dogs (3%) died with no specific treatment information.

The cases that presented complete remission had mainly with unique lesions (75.7%) and fewer number of animals had multiple lesions (24.3%). All dogs that died because of tumor related causes presented multiple extragenital TVT lesions. Surgery was curative in one dog, in the another one the evolution disease was not informed.

4. Discussion

This is the first systematic review about extragenital TVT in dogs that involves a description of a high number of cases in veterinary medicine. In contrast to genital TVT (Huppes et al., 2014; Murchison, 2016; Souza et al., 2017), information regarding modes of

transmission, most common affected organs, response to treatment and prognosis of extragenital TVT are scarce in veterinary literature.

Most of the studies in this review were published after year 2000 (94%), which can be explained by the recent advances in veterinary oncology, improvement in diagnostic tools and increase number of veterinary journals (Huppes et al., 2014).

The Europe had the highest number of reported cases, but this could clearly be a consequence of a region more interested in literature publications than a real higher incidence in this continent when compared to others. In this context, Strakova and Murchison (2014) evaluated the worldwide distribution and prevalence of TVT in dogs and described that Europe have regional variations of prevalence of TVT. Same authors agreed that north and west region of Europe have just isolated cases of TVT or imported from other regions, whereas the south and east have TVT prevalence of 10%.

The data found in this study seem to be similar to the prevalence reported by Strakova and Murchison (2014), since the majority of extragenital TVT was found in Greece (n=35), Turkey (n=4), Portugal (n=3), Italy (n=2) and Romania (n=1). A review of 25 cases of ocular TVT made in Greece (Komnenou et al., 2015) may explain the higher number of cases reported in this country, however this high incidence could be the result of a better documentation of cases.

In a previous study (Strakova & Murchison, 2014) was observed that TVT was endemic in at least 90 countries and its prevalence was equal or over 1% in at least 13 countries in South and Central America, 11 in Africa and eight in Asia. The high prevalence in these areas seem to be related to the tropical weather and poor control of stray dogs that lead to elevated population of young, malnourished, promiscuous and immunologic deficient dogs, which constitute a strong risk factor for TVT transmission (Cohen, 1985; Prez et al., 1998; Siddle & Kaufman, 2015).

The occurrence of extragenital TVT seems to differ of the genital. While extragenital was identified in just four countries in South America, four in Africa and three in Asia, genital TVT was prevalent in many countries, corroborating with Strakova and Murchison (2014). However, this study is based on published cases in scientific literature, which may underestimate the real prevalence of the disease.

The low incidence of TVT cases in the USA was also seen in this study since only three cases of extragenital were reported in this country. TVT prevalence is restricted to the indigenous reserves in Arizona and North Dakota and cases imported from neighbor

countries. Most likely, the main reason for the low occurrence of TVT in USA is because better and more rigorous control of the stray dog population (Komnenou et al., 2015).

In spite of lacking studies regarding extragenital TVT, results this study like breed, sex and age range predisposition were similar than in epidemiologic informations on the genital TVT. Mixed-breed dogs were most commonly affected, as they constitute the most characteristic population of stray dogs (Ganguly et al., 2016).

In this study, the males (56.5%) were slightly more affected than females (43.5%); similar results were found by Strakova and Murchison (2014), who tried to establish the global distribution of canine TVT, collecting information from all around the world. In this sentid, the males could be more affected because of the extragenital TVT mode of transmission (Tella et al., 2004). Most of the extragenital TVT did not involve genital lesions and were transmitted mainly by direct contact of TVT lesions (lick or sniffing), not being necessary sexual contact. On the other side, bitches are more exposed to genital TVT transmission because of continuous and numerous matings with different male dogs during their long estrus period (Murchison, 2016).

Most of the dogs in this study were between one to five years, which it is the period of time with the highest sexual activity and therefore, increased risk of disease transmission (Silva et al., 2007; Ganguly et al., 2016).

In this study, were found high percentage of dogs (68.6%) exclusively with the extragenital form of the disease, without genital involvement. Peixoto et al. (2016) evaluated 203 dogs with TVT and observed that just 23.5% showed exclusively extragenital TVT, 19.2% of animals had genital and other organs affected, and rest of dogs presented only genital TVT. The majority of dogs in this study presented with just a solitary lesion of extragenital TVT and, less than 30%, had more than one site affected. Thus, summing up the data in this study, the most common presentation of extragenital TVT was solitary lesions without genital involvement.

In this research, the external regions of the body identified as the most commonly affected and suspected of direct contact transmission as its main mode of transmission. Most of the dogs with TVT in external organ lacked of genitalia involvement, suggesting that implantation of TVT cells in these dogs came from direct contact with other animals positive to TVT than transmission from genitalia of their selves, according to reports of Huppes et al. (2014).

Internal organs were also affected. Interestingly, 71.4% of animals with TVT in the spleen also presented hepatic involvement, suggesting a common route of dissemination.

Lymph node involvement suggests metastases through lymphatics that may spread TVT cells to other internal organs (Tella et al., 2004), however as TVT cells were also identified in the blood of one patient, were cannot rule out the hematologic route as a route of metastases. Few papers have studied about routes of TVT spreading, like this were proposed some theories that may be involve in the dissemination of TVT to internal organs.

Spreading of TVT through ascendant tumor invasion to urogenital organs was little frequent and affected organs (kidney, uterus, ovary, bladder) had the same number of cases. Females represented 90.9% of the population affected in the urogenital region and this may be explained by the shorter and narrow urethra (Konig & Liebich, 2016) that facilitate ascension of cells to organs like bladder, as it is described in bladder invasion in transitional cell carcinomas. On the other side, males are less predisposed to urethra invasion as we did not find any cases of prostatic TVT.

Renal dissemination most likely occurred through ascendant invasion, hematologic or lymphatic metastasis since all of three cases diagnosed presented also internal organ affection. Similarly, cases of renal commitment reported in literature described concomitant involvement of lungs, liver, spleen, lymph nodes and kidneys (Park et al., 2006) and others of kidneys, liver, spleen and lymph nodes (Silva et al., 2007).

Based on presents results and on previous studies (Park et al., 2006; Silva et al., 2007) hematologic or lymphatic path may be a more feasible route of metastasis to kidneys in cases of TVT. Thus, excluding kidneys, the occurrence of ascendant tumor invasion represents only 3.7% of the total of cases. This information takes relevance since veterinary literature lacks of data on this field.

The results of the present study showed that the majority of cases presented complete remission after a chemotherapy of vincristine and this is in accordance with literature scientific, that suggested vincristine as the treatment of choice in TVT cases (Das & Das, 2000; Gonzales et al., 2000; Brandão et al., 2002; Nak et al., 2005; Silva et al., 2007; Ramadinha et al., 2016). Although were collected information about isolated surgical treatment in two cases of extragenital TVT, researchers disapprove this therapeutic option for the genital and extragenital TVT, as it may occur transplantation of neoplastic cells to areas close or far away from the surgical wound via surgical manipulation (Amber & Henderson, 1982; Idowu, 1984).

The extragenital TVT isn´t directly related to patients with genital TVT and both have good prognosis. Complete remission was a result of chemotherapy (average of seven sessions) in more than 75% of cases. Solitary lesions presented a higher rate of complete

remission than the multiple and few dogs died because of tumor related causes, despite all of them had multiple lesions. These facts lead us to think that solitary lesions could have favorable prognostic value in extragenital TVT. The cases of resistants TVT were not clearly reported in this review, however others chemotherapy drugs can be chosen in cases of resistant tumors (Idowu, 1984; Gonzales et al., 2000).

5. Final Considerations

Based on the applied methodology and the results obtained, it is admitted that the published literature about extragenital TVT came mostly from Europe and South America and most of the cases reported lacked of genital involvement. The mixed-breed dogs were the most commonly affected, just like the males and animals between one to five years-old. The localization of TVT was found to be more common in external organs than internal and ascendant organs. Besides that, a route of ascension infiltration from genital seems to be probable but rare. The vincristine was the most frequently reported chemotherapy drug, presenting high rates of complete remission. Dogs that died because of the tumor, presented multiple masses and did not respond to chemotherapy, thus, further studies are needed to identify prognostic factors about this disease.

Declaration of conflicting interests

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