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Chapter

Canine Transmissible Venereal Tumor: An Infectious Neoplasia in Dogs

Chanokchon Setthawongsin, Somporn Techangamsuwan and Anudep Rungsipipat

Abstract

Canine transmissible venereal tumor is the oldest cancer in dogs and is transplanted via viable cancer cells. This cancer has a specific host, easy transmission, noticeable gross lesions, a predictable growth pattern, an immunologic relative host response, unique molecular characteristics, and is responsive to chemotherapeutic treatment. These points make researchers and practitioners interested in this cancer. Genital cases are noticeable and therefore easier to diagnose and treat than extragenital cases. By contrasting the anatomical features of the two types of cases, we highlight the uniqueness of canine transmissible venereal tumors and discuss the diagnosis, treatment, and prevention of this ancient cancer.

Keywords: canine transmissible venereal tumor, diagnosis, infectious neoplasia, malignancy, treatment

1. Introduction

Canine transmissible venereal tumor (CTVT) is the oldest known contagious cancer in dogs in the world. The first mention of this cancer occurred in the nineteenth century. It is also known as canine infectious sarcoma, canine venereal granuloma, canine transmissible lymphosarcoma, canine round cell sarcoma, and canine Sticker’s sarcoma [1, 2]. CTVT has an etiology like that of other contagious cancers, such as devil facial tumor disease (DFTD), which originates from an abnormal cell line with an unlimited proliferative capacity [3, 4]. CTVT can be transplanted via viable cancer cells that naturally allograft between CTVT-infected dogs and uninfected hosts via physical transfer [4].

Previous studies suggest that CTVT cell lineage might be up to 10,000 years old [5]. The clonal origin of CTVT was proven through the analysis of microsatellite polymorphisms, mitochondria DNA (mtDNA), dog leukocyte antigen (DLA) typing, and genome sequencing. It has been suggested by phylogenetic analysis that CTVT emerged between 4000 and 8500 years ago in Asia [6–9]. CTVT is now a common disease worldwide that has been reported on all inhabited continents. However, CTVT has a higher prevalence in tropical and subtropical regions and is uncommon.
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in North America and Northern and Central Europe, although occasional cases have been reported in imported dogs [5, 10]. An interesting feature of this cancer is that it is usually curable via several protocols. However, metastasis, chemotherapeutic resistance, and death are still reported in CTVT cases in endemic areas, especially in immunosuppressed dogs [1, 11].

2. The carcinogenesis and biological behavior of CTVT

The carcinogenesis of CTVT remains unclear. This cancer may be caused by many sources, but all CTVT cells share the same genetic rearrangement [12]. Specifically, the long interspersed nuclear element-1 (LINE-1) in CTVT cells shows a difference from normal dog cells or host cells [12]. This evidence demonstrates that CTVT clonal evolution grows along the host, and the genetic instability and numerous mutations of CTVT cells give them contagious abilities [6, 8].

Remarkably, CTVT cells are usually transplanted through physical transmission from one dog to another during sexual intercourse. The violent exertions associated with intercourse in both genders are prone to causing genital mucosal damage, which enables the transmission of viable CTVT cells to susceptible hosts. The tumor starts to grow as solitary or multiple nodules at the glans penis or bulbus glandis area in the male dog and on the mucosa wall of the vagina or vulva in the female dog [13]. Cancer cells can affect the mucosa of the external genital organs, skin, and other sites on the body [14–19]. Transplantation occurs individually across the major histocompatibility complex (MHC) between the cancer cells of the CTVT-infected dog and the damaged mucosa of the susceptible dog [1, 2]. CTVT can evade the host’s immunological detection, allowing its worldwide spread as a naturally occurring allograft cancer in dogs because its cells lose the expression of MHC class I and II molecules. The growth of a CTVT mass in the external genital area usually appears within 2–6 months after mating [13]. CTVT was the first tumor to be experimentally transplanted by Novinsky in 1876. The CTVT mass cannot be grown with cells that have been treated with glycerin or cell-free filtrates or cells that have been frozen or heated [13]. Even though this contagious cancer has been described as having only dogs as its specific host, CTVT can be heterotransplanted experimentally by inoculation between dogs (Canis familiaris) and other members of the social canids, such as wolves (Canis lupus), foxes (genus Vulpes), coyotes (Canis latrans), and jackals (Canis aureus) [1]. The transplantation of viable CTVT cells has also been successful in irradiated mice and athymic nude mice as xenografts in a murine model [13]. Experimentally transplanted and naturally transplanted CTVT growth patterns are predictable and clinically characterized by an initial aggressive growth or progressive phase (P-phase), followed by a stable population in the host or stationary phase (S-phase), and then slowly diminishing cancer cells in a regression phase (R-phase) [20]. In the P-phase, CTVT has a rapid growth rate and forms a mass-like cauliflower feature with discharge at the genital area. Histologic examination of the predictable growth pattern of CTVT in the P-phase reveals numerous round-to-ovoid-shaped CTVT cells with an abundance of mitotic figures and few tumor-infiltrating lymphocytes (TILs). The extracellular matrix in the P-phase is rich in the hyaluronan matrix, which may be advantageous for CTVT growth because the hyaluronan creates hydration for the extracellular matrix, which enhances cell proliferation and shields tumor cells against apoptosis [21]. Moreover, the hyaluronan may mask the tumor-associated antigens and MHC antigens on CTVT cell surfaces from the host’s immunosurveillance. Histological
features of CTVT tissues in the S-phase show a decrease in the population of CTVT cells; there are fewer mitotic figures and more apoptotic cells than in the P-phase. In the S-phase, the growth rate of cancer cells is slow. Moreover, TILs increase in the S-phase. In the R-phase, the main cellular population is TILs, and the tumor stroma structure gradually collapses and is replaced by collagen tissue. A key feature of the R-phase is the disappearance of cancer cells [22, 23]. Moreover, vascular stroma and fibrosis increase in the R-phase [11, 23]. During the R-phase, the number of myofibroblasts is higher than in the P-phase. This increase in fibroblast population and tenascin-C extracellular matrix coincides with the increasing number of TILs. These features may be the consequence of the same factor produced by the tumor cells and their microenvironment. During the R-phase, the tumor parenchyma destroys and remodels the tumor stroma. Myofibroblasts and extracellular matrices are related to the R-phase and tissue remodeling of CTVT, which are related to wound healing and stromal reactions of tumors [23].

3. Unique features of CTVT and its diagnostic methods

The CTVT mass frequently manifests in the external genitalia of the dog after transmission through coitus. However, other parts of the body can be affected by this cancer. CTVT can be classified into two types according to its anatomical location: lesions typically located on the external genital area of both male and female dogs are called genital TVT (GTVT), while those found in extragenital areas (including subcutaneous, the mucosa of eyes, and in nasal and oral cavities) are called extragenital TVT (ETVT). The GTVT mass at the external genital area is observed as a cauliflower-like mass feature that is friable tissue with hemorrhage or presents with serosanguinous and hemorrhagic discharge and possible secondary bacterial infection [1, 2, 11, 14–18]. ETVT may be related to social behaviors among dogs because of the means of species communication—for example, licking, sniffing, fighting during the breeding season, and routine socialization. As such, the ETVT type is found more frequently in males than in females due to natural behaviors (Figure 1) [13].

CTVT has remarkable cytogenetic features. There is an aberration in the number of chromosomes of CTVT. Normally, the normal number of chromosomes in the somatic cells of dogs is 78, 76 acrocentric chromosomes, and couple of metacentric sex chromosomes [7, 21]. Conversely, the number of chromosomes in the CTVT cells varies from about 58–59, with 13–17 metacentric and 42 acrocentric chromosomes and no sex chromosome [1, 7, 13]. These cytogenetic features are consistent and unique and are found in both GTVT and ETVT. This chromosome pattern also appears in CTVT cell cultures and in experimental transplantation [24].

CTVT is one of the round cell tumors, according to its cytomorphologic features. GTVT cases are easier to diagnose according to the location (genital areas) and shape (oozing cauliflower-like mass) of their gross lesions [25]. The CTVT mass can be 0.5 to 10 cm in diameter. Histologic examination of the predictable growth pattern of CTVT reveals numerous round-to-ovoid-shaped cancer cells arranged in a diffuse pattern with an abundance of mitotic figures and few TILs, supported by thin trabeculae of fibrovascular tissue [23]. There are some neutrophils, lymphocytes, macrophages, and plasma cells. The CTVT cell passaging tumor showed no change in the histology of the tumor during the experimental passage [13]. However, the atypical anatomical lesions in ETVT cases are more ambiguous to diagnose based on their location and gross lesion because their features depend on their affecting sites.
For example, they perform like a button mass with ulceration when they are located subcutaneously or on the skin. On the other hand, they display irregular shapes in the conjunctiva and oral and nasal cavities. The ETVT tumor must be differentiated from other types, including mast cell tumor, histiocytic tumor, lymphoma, amelanotic melanoma, and poorly differentiated carcinoma, which depends on the anatomical site of the lesion and the characteristics of the histologic examination [25].

Cytologic diagnosis is of great value for easy and rapid on-site diagnosis [26]. As mentioned before, CTVT is one of the round cell tumors, so the main populations of CTVT cells are round-to-ovoid-shaped cells that may originate from the histiocytic system. To improve cytologic knowledge, researchers found that there are three types of cytomorphologic classification of CTVT, which are categorized by the cell morphology of the majority population: (1) lymphocytic type, characterized by more than 60% of round cells, with fine granular cytoplasm, central nuclei, and few intracytoplasmic vacuoles; (2) plasmacytic type, characterized by containing more than 60% of cells with broad cytoplasm, eccentric nuclei, and large amount of vacuoles; and (3) mixed type, presenting both lymphocytoid and plasmacytoid cells, neither of which exceeds 59% [26, 27]. Recently, a study with computerized cytomorphometric analysis of round cells revealed that CTVT had the largest cellular and nuclear size which followed by the histiocytic tumor cell, mast cell tumor, and lymphoma cell. CTVT cell from GTVT case had the largest cellular and nuclear size followed by CTVT cell from ETVT case, histiocytic tumor cell, mast cell tumor cell, and lymphoma cell. According to the CTVT cytomorphologic type, the mixed type had the largest cellular and nuclear size followed by the plasmacytic and lymphocytic type. The researchers have revealed that the plasmacytic type is the most common cytomorphologic type [27, 28]. The plasmacytic type [26–30] and the mixed type [26] are related to malignant behaviors and chemotherapeutic drug resistance.

Figure 1.
Gross lesion of genital TVT (1A, 1B) and extragenital TVT (1C, 1D).
The lymphocytic type shows aggressive behavior less than other types [26]. So, cytomorphologic classification can provide a prognostic for treatment in each CTVT case (Figure 2).

Most canine round cell tumors have been immunohistologically characterized using several tumor markers—for example, cluster of differentiation 3 (CD3), CD79, paired box-5 protein (PAX-5), and protein-tyrosine kinase (c-kit and CD117). Diagnosis and classification using the immunophenotype are more accurate than routine histopathologic examination. However, the cell origin of CTVT is unclear. CTVT has been previously described as lymphosarcoma, a round cell sarcoma, a histiocytoma, and a tumor of neuroectodermal or reticuloendothelial origin [23]. Immunohistochemistry studies revealed that CTVT cells are negative for keratins, α-smooth muscle actin, desmin, CD3, immunoglobulins G and M, γ-light chains, and κ-light chains. These panels ruled out epithelial, smooth muscle, and T- and B-lymphocytes. CTVT cells are positive for vimentin, ACM1, lysozyme, and alpha-antitrypsin (AAT). Lysozyme and alpha-antitrypsin are not expressed by other mesenchymal cells. Moreover, ACM1 is a canine-specific antibody recognized in canine mononuclear phagocyte stem cells. This panel immunophenotypic expression suggests that CTVT has a histiocytic origin because this set of antigens is not expressed by other mesenchymal round cells [23].

CTVT has unique molecular characteristics. CTVT has the rearrangement of the c-myc gene, which is related to the LINE-1 [12, 31]. The LINE-1 is a retrotransposon or jumping gene localized at the 5′ region to the exon of the c-myc locus of CTVT cells. This jumping gene causes destabilization in the entire cellular genome, leads to cellular proliferation and differentiation, and performs the malignant transformation of cells. A rearrangement of the LINE-1–c-myc gene sequence has been used with polymerase chain reaction (PCR) and in situ PCR to diagnose CTVT [6]. The localization of the LINE-1 positive was in the nuclei of CTVT cells; this was not present in other inflammatory cells or CTVT connective tissue. The LINE-1 is inserted in all cases in the same position and presented in the same PCR product size. This method can be performed using fine-needle aspiration (FNA) samples with only 10 nanograms of

Figure 2. Cytomorphology of CTVT cells presents the lymphocytic cell type (arrow) and plasmacytic cell type (star); H&E (40X).
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sample DNA for conventional PCR. The LINE-1–c-myc PCR revealed a diagnostic sensitivity of 100% and specificity greater than 80% [25]. As mentioned before, the CTVT somatic cell lineage is remarkably stable and lacks subclonal heterogeneity despite many genome rearrangements, copy number changes, and retrotransposon insertion [8]. The unique, specific, and constant molecular feature of CTVT is utilized as a definitive diagnostic marker and for applicability in veterinary clinical routines because this feature is found in normal CTVT and vincristine-resistant CTVT cells. Also, the PCR method using FNA samples can be used as a surveillance protocol during and after chemotherapy to determine complete remission status and the appropriate times to stop or restart chemotherapy [11].

4. Treatment of CTVT

CTVT cells respond to many forms of therapy. Historically, CTVT has been treated with surgical excision therapy and followed by several chemotherapeutic cocktails or a combination of chemotherapeutic protocols or radiotherapy. Surgery is chosen for a localized CTVT mass, but it is not recommended in generalized or metastatic cases. Electrosurgery and cryosurgery are optional surgical methods because the tumor is easily transplanted to surgical wounds when using the conventional surgical method. The rate of recurrence after conventional surgery was between 12 and 68% [13]. Surgical methods have a higher recurrence rate than chemotherapy. Radiotherapy was chosen as the therapy for CTVT cases with complete regression within 1–3 treatments of a dose of 10 Gy or 1000 rad. Although radiotherapy is a successful treatment, this method requires sedation for dogs, specialized technicians, and expensive equipment [13].

The original combining protocol was composed of vincristine, cyclophosphamide, and methotrexate. Also, there have been attempted combination protocols, such as cyclophosphamide and prednisolone, vinblastine with cyclophosphamide, vinblastine with methotrexate, and vincristine with ivermectin [13]. After clinical evaluation and development of chemotherapy for CTVT treatment, the use of vincristine, vinblastine, and doxorubicin, as single agents were attempted. The duration of vincristine for complete remission is around 4–6 weeks of intravenous administration at a weekly dose of 0.025 mg/kg bodyweight [11, 32]. CTVT cases are treated using vinblastine intravenously in a dose of 0.1 mg/kg bodyweight on four to six weekly treatments [13]. Moreover, complete remission was also reported within three weeks in the doxorubicin treatment when given intravenously at a weekly dose of 30 mg/m² surface area [19, 32]. Vincristine has been reported as the most effective, safe, and convenient agent for GTVT and ETVT cases. The better response to vincristine treatment may be due to less myelosuppression compared to doxorubicin and no immunosuppression by methotrexate. However, weight loss, mild leukopenia, and gastrointestinal toxicity, such as anorexia, nausea, and vomiting, are common adverse effects of vincristine treatment in less than 10% of cases. An additional complication of vincristine treatment is the extravasation of the drug during administration causing necrotic ulcer lesions of the affected skin [19].

Recently, the combination of vincristine (VCR) and L-asparaginase (LAP) protocol or VCR-LAP protocol has demonstrated an effective treatment result and shorter treatment time than VCR alone. The VCR-LAP combination protocol is given
in alternating weekly doses of 5000 IU/m² of LAP subcutaneously and 0.025 mg/kg of VCR intravenously. The duration of combination protocols is 2–5 weeks, with no evidence of VCR-resistant cases. The short period of treatment provides fewer opportunities for chemotherapeutic drug resistance. Moreover, the combined protocol costs less on average than mono-chemotherapy [11]. A comparative treatment study via a murine model of vascular targeted photodynamic therapy was performed as the new strategy for chemotherapeutic-resistant cases [33]. Moreover, VCR-resistant status is still increasing, not only in ETVT cases but also in GTVT cases [11, 32, 34]. When only partial remission was noted in seven and eight weeks, a 30 mg/m² dose of doxorubicin was administered as mono-chemotherapy every three weeks for a total of five treatments [19]. The duration of doxorubicin treatment was around three applications or two months. In addition, four treatments of vincristine 0.025 mg/kg bodyweight with LAP 10,000 IU/m² every two weeks were also used in resistance cases that showed complete regression [34].

The best thing for veterinarians to keep in mind is that this contagious cancer can be treated with chemotherapy and achieve complete regression. Also, the mono-chemotherapeutic drug VCR can cure this cancer and is recommended as the chemotherapeutic drug of choice for CTVT treatment. Recovery rates are high in more than 90% of cases and have been documented by using VCR at a 0.025 mg/kg body weight dosage over two to eight weeks. The mixed and plasmacytic cytomorphologic types show malignant behavior related to vincristine-resistant and recurrent cases [26]. However, the lymphocytic type has been shown to be less malignant than other types. The larger cell size or the increase in the cellular and nuclear size of tumor cells may demonstrate the survival ability of cells and the progression of tumor grading [35, 36]. Also, the lymphocytic type was found in GTVT cases and was not related to metastasis behavior [26]. According to the anatomical lesion, this can infer that GTVT has a lower malignant behavior than ETVT [11, 26]. In VCR treatment cases, the lymphocytic type had the shortest time to complete regression. The prognosis of treatment with VCR is influenced by the stage of growth, the cytomorphologic type, the size of the tumor, the anatomical site of the mass, and the climate [13, 26, 32]. Recurrence of CTVT was rare because of the effectiveness of chemotherapy. However, some recurrent cases were reported six months after complete remission. So, long-term monitoring after cessation of treatment should be more than six months (Figure 3) [11, 32].

Figure 3.
The lesion at the penis before (3A) and after complete remission (3B).
5. Immunologic relative host response and factors influencing the susceptibility of dogs to CTVT

The CTVT mass grows mostly on male and female external genital areas due to live cell transmission during coitus. The highest risk periods are the estrus and breeding periods. No breed predisposition has been documented, but mixed breed dogs were reported in 41% [19] to 100% [11] of cases. Dogs of any age are susceptible to CTVT. CTVT is most commonly found in intact dogs between two and five years of age. The mean ages of the affected dogs were 3.9–4.5 [13]. GTVT is never found in virgin dogs. Also, the tumor is more common in females than males due to one infected male often interacting with many females, both in breeding kennels and endemic areas [13]. Older dogs showed more ETVT evidence than GTVT, which is more common in intact young adult dogs. Poor body condition scores and immune status might be cofactors in aging dogs with ETVT [11].

Researchers have been interested in and attended the roles of host immunity response in the P-phase and R-phase of CTVT. In experimental transplantation, CTVT can evade immune surveillance and show rapid growth for 12 weeks. The spontaneous regression of both natural and experimental transplantation suggests that the host immune response plays a major role in CTVT. Moreover, immunosuppressed dogs and puppies develop more aggressive CTVT masses that lack TILs, and these masses are rarely eliminated and hardly show complete remission [2]. The differences between the P-phase and the R-phase are the presence and number of TILs. Thus, the complete regression and complete response to treatment may depend on the appropriate immune response of host cells, which is related to the immune status of the CTVT-susceptible dogs. CTVT cells evade immune detection during the transmission period and growth phase by secretion of transforming growth factor β (TGF-β). TGF-β is a multifunctional protein that controls cellular differentiation and proliferation, which acts as a suppression activity of class I and II MHC expression and natural killer (NK) cell activity. Conversely, TGF-β is countered by interleukin-6 (IL-6), which is produced by TILs [20, 37].

CTVT cells show the tumor-associated antigen and shed into the circulation during the P-phase, and this CTVT tumor-associated antigen could no longer be detected after surgical removal of the CTVT mass [13]. This CTVT tumor-associated antigen was detected using antibodies against the antigen during the P, S, and R phases [38]. The amount of this antigen released in the host circulation increased alongside the increase in tumor volume. There is evidence that humoral immunity plays a role in the P-phase. This antigen may be responsible for blocking the host’s immune response in the P-phase. The infiltration, the presence of B cells, and the upregulated expression of the groups of genes related to B cells were mentioned in the signature of acute allograft rejection [13]. Thus, humoral immunity also plays an important role in inhibiting and preventing CTVT tumor development and acute CTVT allograft rejection in many case studies. This emphasizes that CTVT itself has been reported to be antigenic and can evoke tumor rejection in the host’s immunity.

In naturally occurring CTVT, spontaneous regression was also observed, albeit less frequently than in the experimental transplanted CTVT [32]. The dogs that have recovered are immune to reinculcation [1]. Passive immune transfer of post-regression sera to CTVT-bearing dogs has been shown to inhibit and prevent tumor development. Moreover, the growth of CTVT is inhibited in puppies born to dams that are immunized for CTVT before or during pregnancy [2]. CTVT cells have more membrane-bound antibodies in the S and R phases than in the P-phase.
The absence of antibodies in puppies with metastasis suggest the importance of humoral immunity in progression. The metastatic rate is low—less than 20% in GTVT cases [9, 19]. Metastatic cases have been reported in subcutaneous tissues, skin, lymph nodes, eyes, tonsils, liver, spleen, oral mucosa, nasal mucosa, brain, and bone marrow [15, 21, 32, 39]. Although metastasis is not common in CTVT cases, it can be a serious situation and the cause of death.

6. Immunotherapy for CTVT treatment

Recently, researchers have found that inflammation and epithelial cell proliferation may characterize the early response to VCR treatment in the early stage [40]. CTVT in the R-phase after treatment showed that the expression of many groups of genes occurred at the same time, with pathological changes of not only macroscopic features but also microscopic ones. The group of inflammation genes was the most upregulated in the S-phase, and the immunologic groups of genes involved in T-cell, NK-cell, and B-cell function were upregulated in the R-phase. In this late R-phase, there was a loss of CTVT cells and cell migration but an increase in fibrosis that is related to new tissue formation or the healing stage [23, 40]. This finding revealed the process that started with the inflammatory response, epithelial and keratinocyte proliferation and followed by the host T-, NK- and B-cell infiltration, and finished with the cell cycle arrest. In addition, B-cell-related genes, albeit less prominent in quality and expression levels than T- and NK-cell panels, were also progressively upregulated [40]. This is related to previous studies that showed that the infiltration and presence of B-cell was the signature of acute allograft rejection [41].

The interferon (IFN) for neoplasia treatment is initially based on the non-specific activating host immune response. Normally, type I IFN has the ability to inhibit tumor cell growth and induce tumor cell apoptosis in the in vitro studies [42]. During the R-phase of CTVT growth, the IL-6 and interferon-γ or Type II IFN from the host plays a special role in enhancing MHC molecule expression on antigen-presenting cells, activating NK-cell activities, and modulating B lymphocyte responses [20, 37, 43]. An in vitro study of interferon type I for CTVT treatment found that interferonω showed the effect of inhibiting CTVT cell viability in a dose-dependent manner [44]. CTVT case treatment by immunotherapy is of interest to many researchers. Recently, the combination protocol of intratumoral interferon-α2a with VCR shortened the treatment duration when compared with VCR alone [45]. Thus, combining a low-dose chemotherapeutic drug and immunotherapy may be advantageous for CTVT patients because of the initial trigger of inflammation by chemotherapy, synergizes with the activation of the host immune response by interferon. The VCR triggers host interferon signal expression, which induce NK-cell and lymphocyte infiltration. The addition of interferon may enhance the innate and adaptive responses of mononuclear cells and might affect CTVT viability and proliferation. The change in environment and the increase in inflammatory production by local host cells after treatment with VCR may trigger and recruit immune cells. The strong response induced by VCR causes the release of damage-associated molecular patterns from stressed or apoptotic cells as an innate immune response of the host, which induces direct cognition of foreign DLA molecules and ultimately leads CTVT to regression. In addition, this evidence suggests that combining the low dose of chemotherapy with immune checkpoint therapy may help the host immune response against CTVT by inducing the inflammation for tumor regression (Figure 4) [40].
7. The ecology, control, and prevention of CTVT

Stray dogs and poor policy control are the predisposed causes of CTVT transmission [19]. Thus, the control of CTVT transmission is difficult because free-roaming dogs and their intact status represent a reservoir [9, 13]. Prevention is related to government policy, maintenance of spay and neuter campaigns, and animal feeding practices in each country [9]. CTVT cases are found more often in rural areas than in urban areas because of a lack of adequate veterinary services [13]. Currently, CTVT is estimated to be found at a prevalence of 1–10% or more in dogs in many countries on all inhabited continents. CTVT is endemic in at least 90 countries worldwide. The highest prevalence of CTVT was recorded in Belize, where the prevalence was 10–20%. However, prevalence is decreasing in North America and central and northern Europe [9]. New owners and breeders should conduct a careful physical examination before adoption or breeding, especially in imported dogs. Dog licensing laws, spay and neuter encouragement campaigns, and controlling stray or free-ranging dogs should be emphasized to reduce physical contact between infected and uninfected dogs. Also, long-term monitoring of 6–12 months after cessation of treatment should be performed and this practice should be encouraged among veterinarians in endemic areas.

8. Conclusion

CTVT is the only naturally occurring contagious cancer in dogs. This oldest canine cancer spreads through the physical transfer of whole viable cancer cells between hosts. The specific host, transmission, gross lesion, microscopic features, growth pattern, immunologic relative host response, molecular characteristics, and responsiveness to treatment of CTVT are of interest to researchers and practitioners. Genital CTVT cases are visually noticeable and are easier to diagnose and treat than extragenital CTVT cases. The conventional single chemotherapeutic agent VCR has delivered curable treatment in most CTVT cases during 4–6 chemotherapeutic cycles. However, vincristine-resistant cases have been increasing in number. This decade has revealed more treatment options, such as VCR–LAP combination protocol. By contrasting the anatomical features of the two types of cases and the VCR-resistant cases, this paper highlights that the GTVT type is more noticeable and curable than the ETVT type.
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Conflict of interest

The authors declare no conflict of interest.

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