Ginger's Communicable Conundrum

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Class of 2022

Clinicopathologic Conference

July 2nd, 2021

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Introduction

Canine Transmissible Venereal Tumor (CTVT) is the only transmissible tumor affecting dogs, and one of three, possibly four, transmissible tumors affecting any species worldwide. CTVT is most commonly found on the genitals of intact canines, and is transmitted from dog to dog through sexual contact and/or social behaviors. It is one of the oldest noted tumors affecting canines, first described in Europe as far back as 1820 (4). Today, it is considered enzootic worldwide, reported in at least ninety countries, and maintained in populations of free-roaming dogs (7). The prevalence is highest in tropical and subtropical regions, and parts of Africa (4). Antarctica is the only continent where CTVT has not been diagnosed (3). In the United States, CTVT has been reported absent from many regions, but is sometimes found in remote indigenous communities (Arizona and North Dakota), as well in areas near the American-Mexican border. There are also cases found in areas that have dogs imported from Caribbean Islands. Eradication from various geographic regions is linked to the introduction of dog management laws. These laws discourage roaming populations and encourage spay and neutering, which in combination reduce effective contact between affected animals (7).

There are several key features of CTVT that make it unique from other all other neoplasms. This histiocytic round cell tumor is believed to have originated hundreds of thousands of years ago in canine species. The tumor can only be introduced to an individual by transplantation of viable tumor cells on a breached mucosal surface, via sexual contact or social behaviors. CTVT has a clonal origin, meaning all tumors have arrived from a single tumor lineage and share almost identical DNA. There are significant somatic mutations which drive tumor growth and evasion of host immunity. Tumor persistence within the host is achieved through accumulated mutations in pathways related to immune system recognition of self vs.

non-self and initiators and executors of apoptosis (3). CTVT also has the potential to metastasize within the body of immunodeficient individuals at a rate of 5-17% for all individuals affected with the tumor (4, 9).

Individuals presenting with CTVT are typically free-roaming, sexually intact, mature dogs, with no gender predilection, who have lesions most commonly found on the genitals, or less commonly the face (8, 9). These tumors are cauliflower-like pink-to-red nodules, which may exude a serosanguinous fluid, and can measure 1 to 15 centimeters in diameter on mucosal surfaces. The most common complaint from presenting owners is a persistent hemorrhagic discharge. In females, this discharge will not be associated with the estrous cycle (8). Definitive diagnosis is attained through fine needle aspirates or impression smear of the tumor and cytologic identification. Treatment modalities may include surgical excision, and radiation, but most definitive treatment is achieved through chemotherapy (9). Prognosis following treatment is very good to excellent for complete remission.

Signalment, History, & Presentation

Ginger, an approximately three year old female spayed mixed breed dog, presented to Mississippi State University College of Veterinary Medicine Surgery Department on March 8, 2021 for a vulvar mass and left cranial cruciate tear consult. Ginger was adopted from a shelter in Jackson, Mississippi on December 12, 2020 where she had been spayed and diagnosed with a heartworm infection. Her owners noticed a mass protruding from her vulva recently after her adoption, and had a consult with her primary veterinarian on December 23, 2020 where the owners were advised to recheck the mass at a later date for spontaneous regression. The primary veterinarian rechecked the mass on January 5th, 2020 and found that the it was still protruding

from the vulva and scheduled Ginger for a mass removal for January 12th. On January 12th the mass appeared to be regressing, but now was exuding a sanguineous and purulent discharge. Surgery was postponed, and Enrofloxacin was prescribed due to the purulent discharge, Ginger was sent home for further monitoring of the tumor. In March 2021, the owner contacted his primary veterinarian about failure of tumor regression and a recent leg injury. Ginger was diagnosed with a torn left cranial cruciate ligament then referred to the MSU-CVM Surgery Department for a mass excision and TPLO consult.

On initial presentation, Ginger was bright, alert, and responsive, but anxious. She weighed 41 pounds (18.8 kgs) with a body condition score of 5 out of 9, with 4-5 being ideal. Her temperature was 101.7 degrees F, her heart rate was 116 beats per minute, and her respiratory rate was 60 breaths per minute. Cardiopulmonary auscultation revealed no evidence of crackles, wheezes, murmurs, or arrhythmias. Her femoral pulses were strong and synchronous to her heart rate. Her mucous membranes were pink with a capillary refill time of less than 2 seconds. Abdominal palpation revealed no evidence of organomegaly or fluid wave. Peripheral lymph nodes were soft, small, and symmetrical. There was ulcerated and bleeding tissue seen protruding from of her vulva with copious serosanguinous vaginal discharge. When fully exteriorized, the mass was seen to be attached to her vagina and extended cranially. The mass was approximately 6 cm long x 2 cm wide x 2 cm thick. The mass was red, friable, and has an irregular surface with a wide base. On orthopedic examination, Ginger had a 2/5 lameness in the left pelvic limb. Ginger's left stifle had cranial drawer, tibial thrust, pain on hyperextension, medial buttress, and stifle effusion. The right stifle was painful on hyperextension and had very mild stifle effusion, but no instability was appreciated. The right hip had crepitus, and was painful on range of motion, most notably in extension and abduction.

Diagnostic Approach & Considerations

The diagnostic approach for a canine vaginal tumor is selected based on suspected tumor type. This is determined by tumor physical appearance, behavior and statistical probabilities. Canine vaginal tumors are most commonly benign, and include leiomyomas, fibromas, and lipomas. Benign vaginal tumors commonly have a smooth surface, are slow growing, and can be hormone dependent. These tumors also more commonly arise from the vulva rather than the vagina. Malignant tumors are less commonly seen. Malignant vaginal tumors can be leiomyosarcomas, adenocarcinomas, squamous cell carcinomas, hemangiosarcomas, osteosarcomas, mast cell tumors, and epidermoid carcinomas. Malignant tumors have no predilection for location they arise from and can take on variable appearances depending on tissue of origin. Another uncommon vaginal tumor on the differential list is the canine transmissible venereal tumor. It commonly appears bleeding with a friable surface and arises from the vagina rather than the vulva. (10)

The appearance of Ginger's tumor on presentation was not consistent with common benign or malignant tumor types. Her tumor was large, friable and oozed a hemorrhagic fluid, consistent with CTVT. Diagnostic test of choice for identification of CTVT is impression smear cytology of the tumor's surface. Ginger's vaginal tumor cytology revealed a predominant population of cells that exhibited a modest amount of anisocytosis and anisokaryosis. The nuclei were centrally to eccentrically located, had a round to oval shape, a granular chromatin pattern and occasionally had distinct nucleoli. The cytoplasm was basophilic, moderate in amount and had round to oval shaped borders that often contained 2-5 small, discrete perinuclear vacuoles. This cell population was consistent with CTVT.

Due to the diagnosis of CTVT, as well as concurrent heartworm disease, further diagnostic imaging was warranted to rule out metastasis or cardiopulmonary compromise secondary to heartworm disease. Abdominal radiographs revealed no significant abnormalities. Thoracic radiographs showed an enlarged right caudal pulmonary lobar artery and a chronic bronchitis pattern in the lungs, both attributable to her concurrent heartworm infection. Abdominal ultrasound revealed a splenic nodule and a mild medial iliac lymphadenopathy. To rule out metastasis, fine needle aspirates of both abnormalities were taken. The splenic nodule was found to be consistent with extramedullary hematopoiesis and the medial iliac lymph node consistent with lymphoid hyperplasia. Ginger had no evidence of CTVT metastasis or significant cardiopulmonary compromise secondary to heartworm disease. Both her complete blood count and small animal liver profile also showed no significant abnormalities.

Treatment & Management

Treatment options for CTVT include chemotherapy, radiation, and much less commonly, surgery. Surgical excision has not found to be consistently curative and has a tumor recurrence rate of approximately 30-75% . Radiation therapy has shown clinical success, but is not widely used as a primary treatment due to tumor location and radiation side effects. The most definitive treatment option is single agent chemotherapy. (9) Vincristine is the most common chemotherapy agent used, with high success rate of 90-95%. For vincristine-resistant tumors, doxorubicin can be effective as a second choice drug, or radiation therapy can be used as a rescue therapy for chemotherapy resistant tumors. (6) In some cases of CTVT, spontaneous regression is seen within three months of tumor growth due to sufficient development of tumor

immunity via IgG formation. Spontaneous tumor regression is most commonly seen in older immunocompetent animals vs. young and/or immunosuppressed animals. (4, 9)

Vincristine is a vinca alkaloid that inhibits cell replication at metaphase and has cytotoxic activity to disrupt cellular microtubule formation, resulting in apoptosis. Tumor cells treated with vincristine also have reduced production of immune suppressing substances which allows for increased intra-tumor leukocyte infiltration and tumor clearance. When dosed weekly, vincristine achieves plasma levels that effectively penetrate tumor tissues for a long period of time without overall systemic accumulation. On average, complete remission can be achieved after two to eight consecutive weeks of treatment. It is recommended for one to two additional treatments to be administered past tumor resolution. Side effects seen after vincristine administration include ileus, peripheral neuropathy and gastrointestinal upset. Supportive care may be warranted between treatments. However less commonly seen with CTVT, some tumors do not resolve after vincristine treatment, or start becoming larger during treatment. For these resistant tumors, doxorubicin or radiation therapy may result in complete remission. (2, 9)

The treatment protocol chosen for Ginger was single agent chemotherapy using vincristine to be administered weekly until two weeks past tumor resolution. At each appointment a complete blood count was taken to assess white blood cell levels in response to prior chemotherapy, to ensure she was healthy enough to continue therapy. Chemotherapy and communicable disease precautions were applied to her at home care. These include minimizing human contact for three days post drug administration to reduce chemotherapy exposure, and keeping Ginger separate from other dogs to prevent the spread of her cancer to other dogs. Ginger was prescribed Cerenia and metronidazole to manage adverse effects of chemotherapy while at home. Ginger tolerated chemotherapy well and never used these supportive care drugs.

Pathophysiology

Canine transmissible venereal tumor transmission is similar to allograft transplantation. Successful transmission occurs when a sufficient population of live tumor cells are introduced from one dog to a damaged mucosal surface on another dog. (3, 9) Unlike allografts, these tumor cells have a different major histocompatibility complex (MCH) than the host's cells, which should result in rapid immune response and destruction. However, there are alterations within the tumor's DNA that contribute to host immune system evasion. These DNA mutations result in loss of MCH expression on the surface of cells as well as formation of immunosuppressive cytokines. (5) Once a dog becomes infected with these tumor cells, the cells undergo a period of rapid growth lasting as long as three months; this phase is often marked with a hemorrhagic discharge (4, 5). The tumor then becomes static and remains relatively unchanged in size. Eventually the tumor goes through a regression phase. The regression phase can result in complete remission, or the tumor can lay dormant for a period of time. (5) Individuals in complete remission have circulating anti-tumor immunoglobulins that reduce the likelihood remission or contracting CTVT again. Uncommonly these tumors will metastasize. CTVT metastasis most commonly affects regional lymph nodes, but truly has the potential to travel anywhere in the body.

The clinical signs seen in dogs affected with CTVT are dependent on the size and location of the tumor(s). The most common clinical sign owners notice first is the bright red, hemorrhagic discharge coming from the genitals during the growth phase. The tumor then will grow to be more visible, protruding from orifices. Secondary urinary tract infections are a common sequela and contribute to a foul odor around the genitals. As the tumor grows, the genitalia become more uncomfortable, and many dogs will often excessively clean themselves

perpetuating secondary infections as well as creating ulcerations on the tumor. Very large genital tumors will cause dysuria, constipation, paraphimosis, and refusal to mate. Non-specific clinical signs seen affected dogs include lethargy, weakness, anorexia, and weight loss. Sometimes dogs can be affected on the mucous membranes of the face; these tumors present in or around the mouth, nasal cavity or even conjunctiva. Facial tumors can impede airways causing dyspnea as well as anorexia. (4)

Tumor behavior can seem to differ between affected individuals. Some tumors are more aggressive, while in others CTVT will regress on their own. Some tumors are more resistant to therapy, while others reach complete remission. These differences may be explained by different cellular subtypes. Subtypes are based on cellular appearance, and consist of lymphocytoid, plasmacytoid and mixed types. The lymphocytoid subtype consists of round cells with granular cytoplasm, few vacuoles, and can have two nuclei. The plasmacytoid subtype is mostly made up of ovoid cells with more cytoplasm, fewer vacuoles, and a singular central nucleus. Chemotherapy resistance has been linked to the plasmacytoid subtype because it has a P-gp transmembrane protein, which acts as an efflux pump for vincristine and doxorubicin, reducing effective drug levels inside the tumor cells. These plasmacytoid subtypes tend to be more aggressive; however, the immunocompetence of the affected animal may play a more significant role in tumor behavior. (1)

Case Outcome

Ginger was diagnosed with CTVT and started chemotherapy treatment on March 9, 2021. Ginger's chemotherapy protocol consisted of weekly vincristine treatments. She was sent home with supportive care drugs, maropitant and metronidazole, which she never needed to use. After

her first round of vincristine, Ginger's tumor had reduced in size approximately 50% and it was no longer visible without exteriorizing it from the vulva. After the second round vincristine, the tumor had reduced 75% from the original size. Following five rounds of vincristine treatments, Ginger's tumor could no longer be appreciated visually or by palpation, she was considered to be in remission. However, her chemotherapy protocol stated for her to continue vincristine treatments two more treatments after remission.

On April 20, 2021 Ginger presented for her seventh, and last, vincristine injection. At that appointment the tumor had once again become palpable, measuring approximately 5mm in length. That day she received her seventh vincristine treatment which was at higher dosage than she received at her prior injections. This dose escalation was used in efforts to get a better response out of the vincristine before deciding to change chemotherapy agents. Ginger was then scheduled to come back in one week to reassess the tumor re-growth and to change her chemotherapy agent to doxorubicin if it was found to be remaining. One week later the tumor was the still approximately 5mm in length, Ginger was then administered her first round of doxorubicin. On May 18, 2021, one week after her doxorubicin treatment Ginger presented for her recheck, and the tumor had mostly regressed. There was a 1-2mm mass present in the region of the tumor. The remaining tissue was determined to most likely be remnants of the tumor, but could not be ruled out as being scar tissue from previous inflammation. Due to a low likelihood of tumor regrowth and metastasis, Ginger's owners decided to stop chemotherapy and pursue future treatment of her torn cranial cruciate ligament and heartworm infection.

Conclusion

When presented with growths on the genitalia or face, CTVT should be on the list of differential diagnoses. Accurate patient history and physical exam can aid in ruling in or out CTVT. Definitive diagnosis is through positive identification of cells on tumor cytology. Prognosis is good for complete remission, commonly achievable via single agent chemotherapy using vincristine. Other treatment modalities, doxorubicin and radiation therapy, can be used for refractory cases. In some animals, spontaneous regression can occur and result in complete remission with tumor immunity. Appropriate canine roaming and population control regulations significantly reduce tumor incidence within those geographical areas.

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