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Concomitant Occurrence of Transmissible Venereal Tumor, Pyometra, and Pregnancy with Cleft Lip and Palate in a Crossbreed Bitch: A Case Report

(LAPORAN KASUS: KEJADIAN BERSAMAAN TUMOR KELAMIN MENULAR, PYOMETRA, DAN KEBUNTINGAN DENGAN JANIN SUMBING DAN LANGIT-LANGIT MULUT BERCELAH PADA ANJING PERANAKAN)

Aloysiana Margaretha[1], Marissa Divia Dayanti[1], Kevin Tri Tama[1], I Wayan Batan[2]

[1]Professional Programme of Veterinary Medicine Student,
[2]Veterinary Clinical Diagnosis, Clinical Pathology and Radiology Laboratory,
Faculty of Veterinary Medicine, Udayana University,
Jl. Sudirman, Sanglah, Denpasar, Bali, Indonesia, 80234;
Telp/fax: (0363) 223791
e-mail: aloysianamargaretha@gmail.com

ABSTRACT

A female crossbreed dog, estimated to be four years old with a bodyweight of 9.5 kg was diagnosed with a transmissible venereal tumor (TVT). Cytological examination showed the shape of lymphocytic and plasmacytic cells which are consistent with the transmissible venereal tumor cell findings. Treatment was done by *en bloc* ovariohysterectomy, surgical excision of the tumor mass, and chemotherapy using vincristine sulfate. During the surgery, it was found that apart from being infected with TVT, the dog was also observed with pyometra and found to be pregnant. The dog had one puppy with a birth defect (cleft lip and palate) and died a few hours later. Postoperatively, dogs were given a combination of dexamethasone and diphenhydramine (0.2 mg/kg BW and 4 mg/kg BW intramuscularly/IM) and antibiotic cefotaxime (22 mg/kg q12h IM). Two days after the surgery the dog showed an improvement in its condition, oral drugs began to be administered and injection drugs were stopped. Treatment was continued with the administration of antibiotic cefadroxil (22 mg/kg BW q12h per orally/PO) and metronidazole (15 mg/kg q12h PO) for five days along with the administration of multivitamin Nutrilite Double X-Phytonutrient® one capsule/day for seven days. A week after surgery the dog was sent home without additional medication. The dog is scheduled for chemotherapy the following week.

Keywords: dog; cleft lip and palate (CLP); pyometra; transmissible venereal tumor (TVT)

ABSTRAK

Seekor anjing peranakan berkelamin betina dengan bobot 9,5 kg diperkirakan berumur empat tahun didiagnosis terinfeksi transmisible venereal tumor (TVT). Hasil sitologi yang didapatkan menunjukkan bentuk sel limfositik dan plasmasitik sesuai dengan gambaran sel TVT. Penanganan dilakukan dengan pembedahan eksisi massa tumor dan *en bloc* ovariohisterektomi serta kemoterapi menggunakan vinkristin sulfat (0,025 mg/kg BB). Pada saat pembedahan, ditemukan bahwa selain terinfeksi TVT, anjing juga mengalami pyometra dan ditemukan sedang bunting. Anjing memiliki satu anak dengan cacat bawaan (bibir sumbing dan langit-langit mulut bercelah) dan mati beberapa jam setelahnya. Pascaoperasi, anjing diberikan kombinasi deksametason dan difenhidramin (0,2 mg/kg BB dan 4 mg/kg BB intramuskuler/IM) serta antibiotik sefotaksim 22 mg/kg, q12h, IM. Dua hari pascaoperasi, anjing sudah menunjukkan perbaikan kondisi, obat oral mulai diberikan dan obat injeksi dihentikan. Pengobatan dilanjutkan dengan pemberian antibitiotik sefadroksil (22 mg/kg BB, q12h per oral/PO) dan metronidazol (15 mg/kg q12h PO) selama lima hari serta pemberian multivitamin Nutrilite

Double X-Phytonutrient® satu kapsul/hari selama tujuh hari. Seminggu pascaoperasi anjing dipulangkan tanpa pemberian obat tambahan. Anjing dijadwalkan untuk kemoterapi pada satu minggu selanjutnya.

Kata-kata kunci: anjing; bibir dan langit-langit mulut bercelah; pyometra; tumor kelamin menular

INTRODUCTION

Veterinarians have often found lesions in the bitch's reproductive tract during their practice, and these lesions can develop at any stage of the animal's reproductive life (Ortega-Pacheco *et al.*, 2012). According to Costa *et al.* (2019), the most common reproductive diseases affecting bitches were pyometra (48.8%), dystocia (13.6%), and transmissible venereal tumor (TVT) (12.6%). Canine transmissible venereal tumor (CTVT) is also known as transmissible venereal tumor (TVT), sticker's sarcoma, sticker tumor, contagious venereal tumor, transmissible lymphosarcoma, venereal granuloma, infectious granuloma, canine condyloma, infectious sarcoma, and contagious lymphosarcoma (Prasad *et al.*, 2007). Transmissible venereal tumor is a reticuloendothelial tumor that mainly affects the external genitalia, specifically the vagina in bitches and the prepuce of penis in male canines. In bitches, the most common lesions occur in the posterior part of the vagina, especially at the vestibulovaginal junction. Due to this deeper location, the growth may not be visible. However, in some cases, the mass is large enough to protrude from the vulva (Milo and Snead, 2014). These tumors are transmitted by contact of live tumor cells with the mucosa (Drumond, 2013).

The incidence of these tumors has been reported in several areas around the world. However, it is considered endemic in many tropical and subtropical countries with a free-roaming stray dog population, which allows continuous local infection because of the uncontrolled free-roaming dog population and lack of effective treatments (Abeka, 2019; Hantrakul *et al.*, 2014). In Bali, TVT cases are reported every year and there were 55 cases in the period 2006-2010 which commonly affect free-roaming local dogs in the streets (Dharma *et al.*, 2010). Dogs of all breeds, ages, or genders are susceptible to infection. Unlike other genital tumors that tend to occur in older dogs (over 10 years of age), TVT in dogs over one year of age is at higher risk in endemic areas and tends to occur most frequently in dogs two to five years of age (Das and Kumar, 2000; Milo and Snead, 2014).

The diagnosis of TVT is made by looking at the physical examinations of the tumor and confirmed by cytology or histopathology (Drumond *et al.*, 2013; Hantrakul *et al.*, 2014). Cytological methods are generally used to diagnose tumors because they are easy, painless,

and less time-consuming than biopsies (Amaral *et al.*, 2007). Several therapies, including surgery, chemotherapy, immunotherapy, and radiotherapy, have been applied for the treatment of TVT. There is also a report on the utilization of the oncolytic virus for TVT therapy, but the result is not convincing (Sewoyo and Kardena, 2022). Chemotherapy with vincristine sulfate followed by surgery is the most effective method of treating venereal sarcoma compared to single surgical therapy or therapy with vincristine sulfate alone (Athar *et al.*, 2001; Laksmi *et al.*, 2019).

Pyometra is a pathological condition of the uterus in which there is an accumulation of purulent semisolid-liquid substance inside the uterus of intact bitches (Kumar and Saxena, 2018). The diagnosis is based on case history, physical examination, and laboratory analyses often combined with radiography and/or ultrasonography of the uterus and ovaries. Clinical signs vary depending on severity of the disease (Jitpean *et al.*, 2014). Pyometra in dog or canine pyometra is commonly reported on bitches from four to sixteen years, but most common at the age of 7,5 years with regular and repeated estrous cycle (Kumar and Saxena, 2018). Adult female dogs aged 10 years often get pyometra with an incidence rate of 25%, but young dogs who have never bred or who have given birth several times can also get this disease (Gibson *et al.*, 2013). One of the risk factors of pyometra is reduced myometrial contraction, this happens in the dog during diestrus phase (progesterone effect) in the gestation period (Risso *et al.*, 2014). Another factor, such as changes within the endometrium, which are secondary to glandular hyperplasia and cystic degeneration, can lead to pyometra. Also, dysfunction of the ovaries often contributes to changes in the uterus which can develop into pyometra (Kempisty *et al.*, 2013). This case report described the rare incidence of TVT, pyometra, and pregnancy in dogs that occur at the same time, treated with ovariohysterectomy, surgical excision of tumor mass, and followed by chemotherapy.

CASE REPORT

Signalement and Anamnesis

A female crossbreed dog named Cookie, estimated to be four years old with a bodyweight of 9.5 kg was brought to the Bali Veterinary Clinic Pererenan, Kuta, Badung, Bali on January 26, 2022. The dog was a stray dog and the client who brought the patient was not the owner of the dog. The dog was brought in because of hair problems (matted hair) and vaginal enlargement. The history of deworming and vaccination is unknown.

Clinical Finding

On physical examination, the general condition appeared to be normal besides dirty and matted hair. The dog had aggressive and cautious behavior, heart rate (HR) and respiratory rate (RR) were normal, had a temperature of 38.8°C, also a capillary refill time (CRT) under two seconds with pink color mucosa. During the examination, vaginal enlargement was obvious and when the vagina was exposed, a cauliflower-like mass was seen, which was consistent with the transmissible venereal tumor (TVT) findings (Fig. 1) and there was no vaginal discharge around. Abdominal palpation showed no change. In addition, for other clinical examinations such as limbs, musculoskeletal, nerves, circulation, respiration, digestion, mucosa, and lymph nodes, no changes were found.

Figure 1. The unfolded vagina shows the mass looks like a cauliflower-like mass and reddish (red arrow).

Laboratory Diagnosis

Supporting examinations are carried out to assist in determining the diagnosis. In this case, cytological examination was performed. The client who brought the patient to the clinic refused to do other supporting examinations such as a complete blood count (CBC) and ultrasound (ultrasonography) which had been suggested due to lack of funds.

On cytological examination, samples were taken through a direct vaginal swab and stained with Giemsa stain. The results showed the shape of the cells in accordance with the transmissible venereal tumor (TVT) findings. Lymphocytic cells, plasmacytic cells, and white blood cells were found, but lymphocytic cells were more dominant than plasmacytic cells (Fig. 2). Lymphocytic cells are round, the cytoplasm is small and slightly basophilic with well-defined margins, round and centrally located nucleus. Meanwhile, plasmacytic cells are oval, eccentric nuclei and larger cytoplasmic ratio than the nucleus.

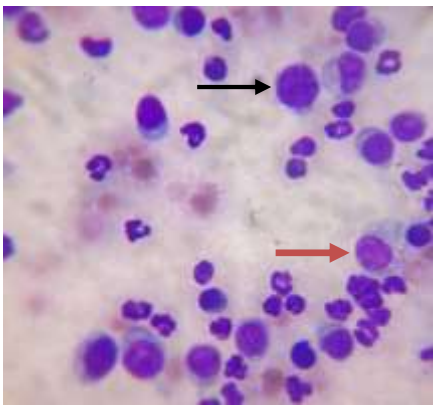

Figure 2. Lymphocytic (black arrow) and plasmacytic (red arrow) morphology cells from a transmissible venereal tumor on cytological examination. White blood cells were also seen (Giemsa, 1000x).

Diagnosis and Prognosis

Based on the results of anamnesis and clinical examination carried by cytological examination, the diagnosis is that the dog has a transmissible venereal tumor (TVT) infection with a good prognosis.

Treatment

The first treatment was bathed and shaved due to matted hair. Furthermore, because the client refused to do a complete blood count, the patient's condition was stabilized overnight before performing surgery the next day. The surgery performed was ovariohysterectomy and surgical excision of the TVT mass. Ovariohysterectomy was performed due to prevent metastases (Ucmak *et al.*, 2019) of TVT into the internal organ and to control the population since it is a stray dog. Prior to surgery, the dog was given xylazine as a premedication (Xyla®, PT. Tekad Mandiri Citra, Bandung, Indonesia) 3 mg/kg BW, intramuscularly (IM), and 10 minutes later was induced with ketamine (Ket-A-100®, AgroVet, San Luis-Lima, Peru) 15 mg/kg BW, IM. During the surgery, it was found that apart from being infected with TVT, the dog was also observed with pyometra and found to be pregnant (Fig. 3b). The dog had one puppy with a birth defect specifically cleft lip and palate (Fig. 4), then died a few hours later. Furthermore, the tumor mass on the genital was removed by excision until the entire vaginal area was clear from the tumor mass. Subsequently, chemotherapy was continued with vincristine sulfate (Vincristine Sulfate®, PT Sanbe Farma, Bandung, Indonesia) at a dose of 0.025 mg/kg BW intravenously (IV) and repeated every week for three weeks.

Postoperative management was carried out by providing a combination therapy of anti-inflammatory dexamethasone (Dexatozoon®, PT. Wonderindo Pharmatama, Jakarta, Indonesia) at a dose of 0.2 mg/kg BW IM, antihistamine diphenhydramine (Vetedryl®, PT.

Duta Emperor Pharmacy, Solo, Indonesia) 4 mg/kg BW q24h IM, and antibiotic cefotaxime injection (Cefotaxime®, PT Dankos Farma, Jakarta, Indonesia) at a dose of 22 mg/kg BW q12h IM. Two days postoperative, the dog showed condition and appetite improvement. The oral medication was started and the injectable medicine was discontinued. Antibiotic cefadroxil monohydrate (Cefadroxil®, PT Dankos Farma, Jakarta, Indonesia) at a dose of 22 mg/kg BW q12h per orally (PO) and metronidazole (Metronidazole®, PT. Sejahtera Lestari Farma, Pasuruan, Indonesia) at a dose of 15 mg/kg BW q12h PO continue given for five days. In addition, the dog was given a multivitamin (Nutrilite Double X-Phytonutrient®, PT Amindoway Jaya, Jakarta, Indonesia) 1 capsule q24h PO for seven days. A week after surgery the dog was sent home without additional medication.

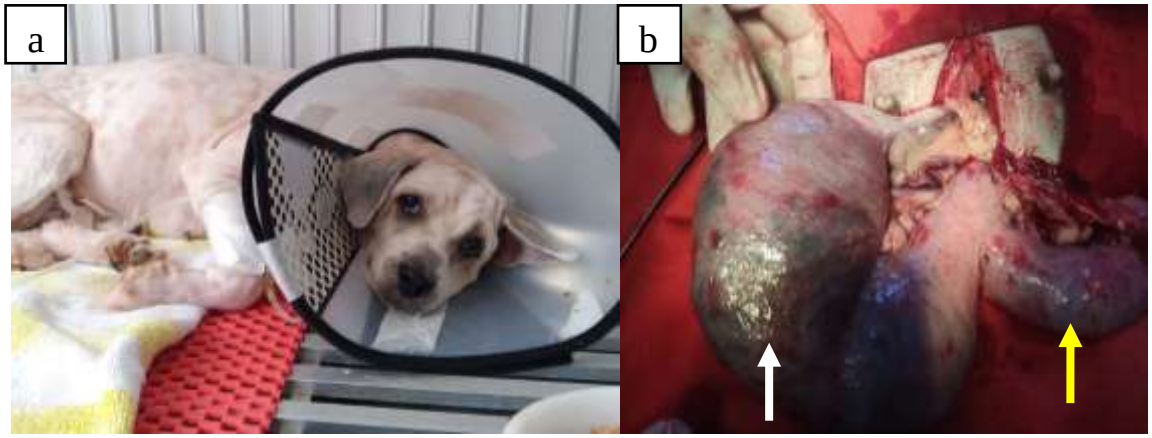

Figure 3. The dog after ovariohysterectomy surgery (a), and uterus with pyometra (white arrow) and pregnancy (yellow arrow) (b).

Figure 4. Puppy with Cleft Lip and Palate (CLP) (White arrow).

RESULTS AND DISCUSSION

Transmissible venereal tumor (TVT) is a contagious, sexually transmitted tumor commonly found in dogs. A high incidence of TVT is associated with free-roaming dogs in

large populations (Hantrakul *et al*., 2014). A presumptive diagnosis of canine TVT is often made based on the combination of epidemiological factors (young-to middle-aged sexually active dogs living in an endemic region) and the location of the tumor (genitalia involvement) (Milo and Snead, 2014). The diagnosis in this case was based on anamnesis and clinical findings supported by cytological examination. In this case, the animal is a street dog located in Denpasar, Bali, an area with a tropical climate. The dog, estimated to be four years old with clinical findings, showed an enlarged, cauliflower-like mass in the vagina. Laboratory diagnosis, in this case, was done by cytological smear and the client did not allow us to carry out other supporting examinations such as CBC, USG, or x-ray. The use of a cytology examination for the diagnosis of neoplasia is recommended because it is considered more accurate than a histopathological examination, cytological examination has been considered important for the diagnosis and monitoring of treatment of transmissible venereal tumors (Montoya-Flórez *et al*., 2013). In addition, a cytology smear is preferred over biopsy for establishing the diagnosis of TVT because it is minimally invasive, inexpensive, and highly sensitive (Milo and Snead, 2014).

On cytological examination, TVT was divided based on morphological differences in the dominant cell types such as lymphocytic, plasmacytic, or mixed. In lymphocytic cell tumors (60% or more TVT cells are round), most of the cells have round morphology, scanty cytoplasm, and finely granular, rounded, and centrally located nuclei. In the plasmacytic cell tumor type (60% or more of the TVT cells are ovoid), most of the cells have an ovoid morphology, abundant cytoplasm, relatively small nuclei, and are eccentric. While in mixed cells, it is a combination of lymphocytic and plasmacytic cell types, where none exceeds 59% of the total (Birhan and Chaine, 2015; Montoya-Flórez *et al*., 2013). In this case, the results of the cytology smear were not quantitatively calculated, but both types of cells were found. Plasmacytic TVT was shown more aggressive than the lymphocytic form (Amaral *et al*., 2004). The plasmacytic type is more common in metastases and recurrent lesions, where the probability of invasion is higher in TVT with predominant plasmacytic cells (Montoya-Flórez *et al*., 2013). The differential diagnosis includes round-cell tumors such as lymphoma, plasma cell tumor, and mast cell tumor (Da Silva *et al*., 2014).

Treatment was done by *en bloc* ovariohysterectomy, surgical excision of the tumor mass, and chemotherapy using vincristine sulfate. During ovariohysterectomy, it was found that apart from being infected with TVT, the dog also suffered from pyometra and appeared to be pregnant. The condition of the uterus was inflamed with accumulation of sanguinopurulent

substance. Afterward, *en bloc* ovariohysterectomy was performed. Pyometra can be defined as a pathological condition of the uterus in which there is an accumulation of purulent semisolid-liquid substance inside the uterus of intact bitches, generally during postprogesterone dominant phase of estrous cycle (Kumar and Saxena, 2018). The diagnosis of pyometra is based on a case history (anamnesis), physical examination, and laboratory analysis, which is often combined with radiographs and/or ultrasound of the uterus and ovaries. However, in this case pyometra was not detected before surgery because the owner refused to do other supporting examinations. Therefore, no other supporting examinations were carried out to confirm the diagnosis of pyometra.

The clinical signs of pyometra vary depending on the severity of the disease (Jitpean *et al.*, 2014). Clinical signs commonly present in pyometra include depression, anorexia, polydipsia or polyuria, vomiting, and vaginal discharge. In cases of pyometra without vaginal discharge, it may be more difficult to recognize the disease at an early stage because most of the other signs of the disease are non-specific (Jitpean *et al.*, 2016). Clinical signs of pyometra were not observed because the dog is a street dog and if there was a vaginal discharge, diagnosis of pyometra will be difficult because the dog was also infected with TVT. However, during the stabilization before surgery, no vaginal discharge was observed.

Pyometra is classified as open-cervix (with vaginal discharge) and closed-cervix (without vaginal discharge) based on cervical patency for drainage of purulent uterine fluid; however, closed-cervix pyometra is a more serious condition, which needs surgical intervention because it can cause sepsis and can be fatal (Jitpean *et al.*, 2016). In this case, because no vaginal discharge was observed, it could be an indication of closed cervix pyometra. Closed cervix pyometra is dangerous and can cause sepsis, peritonitis, and most severe can cause death (Baithalu *et al.*, 2017). Closed-cervix pyometra does not give any general signs at the beginning, these appear only after intoxication with pathogens. When severe intoxication occurs, the body temperature rises, the abdomen can be distended, and the integument becomes tense (Kempisty *et al.*, 2013).

The information about pyometra and concurrent pregnancy in dogs is limited. However, reports according to Risso *et al.* (2014) confirmed that it is possible for a bitch to have both pyometra in one uterine horn and successful pregnancy in the other uterine horn with proper medical treatment. In this case, the puppy of the infected dog with TVT and pyometra was removed by *en bloc* ovariohysterectomy and was found to be alive. Unfortunately, a few hours later the puppy did not survive and died. *En bloc* ovariohysterectomy was performed to

remove neonates immediately. *En bloc* ovariohysterectomy was chosen instead of the traditional caesarian section because the pyometra-infected uterine horn was ligated and pregnancy was recognized on other uterine horn after it was exposed. Unlike traditional cesarean section, this technique involves ovariohysterectomy or removal of the uterus and ovaries first and then the removal of the fetus outside the abdominal cavity (Traas, 2008). The incidence of pyometra is possible due to bacteria infection during pregnancy. Pregnancy causes the endometrium to thicken, increase secretory gland secretions, and stimulate blockage of cervical uterus (Rahayu *et al.*, 2021). The secretions from glandular proliferation in the endometrium can initiate pyometra development (Voorwald *et al.*, 2012). Pregnancy is influenced by progesterone which can cause special activity in the immune system, modulate the action of T lymphocytes and be able to suppress the function of T cells (Maciel *et al.*, 2014). Estrogen increases the growth of uterine cells and blood vessels in the endometrium. It increases the sensitivity of the uterus and the reaction to progesterone. Progesterone causes the secretions of the endometrium and uterine gland to proliferate, reduce myometrial contractions and induce closure of the cervix. The common bacteria found in a healthy bitch's uterus represent the bacterial flora of the vagina and cervix (Fieni *et al.*, 2014). Pyometra occurs as a result of an abnormal response of the endometrium towards progesterone and exposure to bacterial contamination in intact female dogs. At the same time, continued secretion of estrogen from the ovaries causes dogs to show signs of proestrus and estrus and to mate with stray dogs. In this case, the dog is a stray dog that most likely mates with other stray dogs that have been infected with TVT. It is difficult to control since the stray dogs serve as a reservoir. However, there are ways for helping to control the transmission such as; managing the number of free-roaming dogs, maintaining strict spay, neuter practices and perform effective treatment of TVT (Abeka, 2019). In this case, the dog is estimated to be four years old. TVT in dogs tend to occur most frequently in dogs two to five years of age (Milo and Snead, 2014).

The fetus was born with cleft lip and palate (CLP) or labiopalatoschisis (Fig. 4). CLP is caused by either genetic or environmental factors or a combination of both. These causative factors interfere with the morphogenesis process, causing malformations/dysmorphology during palatogenesis. In this case, it is also possible that environmental factors of fetal growth are also the cause. Environmental factors include abnormalities in the amniotic sac and uterus, maternal metabolic diseases, viruses, and chemicals administered to the mother, and maternal exposure to chemical or physical environmental pollutants. But, the interaction between

genetic and environmental factors is still unknown (Moura and Pimpão, 2017). Puppies born to previous carriers are generally also immune to subsequent tumor challenge (Abeka, 2019). A case report by Ayala-Díaz *et al.* (2017), confirmed a bitch with few weeks of pregnancy had been infected with transmissible venereal tumor underwent hysterectomy and salpingo-oophorectomy but there is no further information about the fetus or the puppy. The mechanism of the underlying cause of the association of fetal defect and TVT or pyometra is unkown. This case is the first report of concominant occurrence of TVT, pyometra, and fetal defect (CLP) in a dog.

The dog was sent home after showed good condition a week after surgery and chemotherapy. Vincristine sulfate chemotherapy was given twice (after surgery and a week after postoperative). Treatment of TVT that begins with surgical intervention requires only 2-3 times of chemotherapy with vincristine sulfate, recovery will occur faster and without recurrence (Athar *et al.*, 2001; Laksmi *et al.*, 2019). As an addition, diagnostics must consider status permormance, tumoral stage and clinical stages as well as the capacity of the owner to follow to the medical directions before and after treatment (Ayala-Díaz *et al.*, 2017). The typical course of vincristine treatment is four to eight weeks of intravenous administration at 0.025 mg/kg body weight (BW) (Sudjaidee *et al.*, 2012), but it depends on the severity of TVT and the dog's resistance to chemotherapy (Laksmi *et al.*, 2019). Tumor regression was clinically evident within the first week of chemotherapy. A complete remission usually takes 2-8 injections (Tella *et al.*, 2004). Ideally, chemotherapy for this dog was planned to be administered for 3 times. However, the owner was not able to follow the medical directions due to insufficient funds.

The prognosis for TVT disease is good. Even in the case of metastases, the cure rate is more than 90% (Abeka, 2019). Chemotherapy is given to prevent tumors from metastasizing to other tissues or organs and to prevent tumors from recurring (Laksmi *et al.*, 2019). Metastases are very rare (less than 5-25% of cases) and when they occur, mostly affect the lymph nodes (Milo and Snead, 2014; Birhan and Chanie, 2015). These metastases are often considered mechanical extensions of the primary tumor. Metastases have been reported in the inguinal lymph nodes, but can also be seen in the skin, brain, eyes, liver, spleen, testicle, and muscle (Abeka, 2019). In addition, many of the reported cases of metastasis are actually mechanical extensions of the growth or either auto-transplantation or hetero-transplantation to the skin, cervix, uterus, corpus uterus, and fallopian tubes from the tumor on the external genitalia (Birhan and Chanie, 2015). In young or immunocompromised dogs, tumors may have

a greater tendency to metastasize (Martins *et al*., 2005). In contrast, dogs who had recovered from TVT and puppies born from infected dogs were less susceptible to the disease. Dogs that have been recovered from CTVT have serum transferable immunity to re-infection (Birhan and Chanie, 2015).

CONCLUSION

Diagnosis of transmissible venereal tumor (TVT) with cytology is considered an important and non-invasive method. In this case, bitch infected with TVT and pyometra was treated surgically and continued administration of vincristine sulfate twice as chemotherapy, had shown improvement in its condition and resulted in a good recovery after one week postoperative. This case report is the first report of concomitant of TVT with pyometra and pregnant with cleft lip and palate puppy.

SUGGESTION

Education to clients is very important to provide further information about the patient's condition and the actions that need to be taken to maximize the patient's recovery. In addition, the consequences of each treatment option also need to be re-educated to the client.

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