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Cystic endometrial hyperplasia- pyometra complex in a mastectomized Boerboel bitch following tamoxifen administration

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Abstract

Tamoxifen is a non-steroidal, anti-estrogenic and selective estrogen receptor modulator commonly used as adjuvant chemotherapy in humans with breast cancer and occasionally in dogs following mastectomy. This report presents a case of cystic endometrial hyperplasia-pyometra in a dog following oral administration of the tamoxifen. A 4-year-old intact nulliparous Boerboel bitch presented at Veterinary Teaching Hospital, Federal University of Agriculture, Abeokuta. It was diagnosed with mammary carcinoma of the right cranial lumbar mammary gland. Mastectomy was performed followed by oral administration of Tamoxifen (10mg daily) for six weeks as adjunct chemotherapy. Eight weeks after, the owner reported that the bitch was lethargic, anorexic and had a purulent vaginal discharge. Abdominal ultrasound revealed cystic endometrial hyperplasia. Results of complete blood counts showed neutrophilic (absolute neutrophil count = $19.5 \times 10^3/L$) leukocytosis (total leukocyte count = $24.9 \times 10^3/L$), while bacterial culture yielded moderate growth of *Staphylococcus aureus*, which was sensitive to Ciprofloxacin, Ofloxacin, Sparfloxacin and Gentamycin. The bitch was treated with 400µg of Misoprostol and 500mg of Ciprofloxacin twice daily for two weeks. Ovariohysterectomy (OVH) was performed using a ventral midline approach when no significant improvement was observed from medical treatment. The dog improved significantly after ovariohysterectomy and was discharged one week after OVH. It was concluded that, although tamoxifen is routinely used as adjuvant chemotherapy following mastectomy, more research is required to evaluate its safety in intact bitches.

Keywords: Cancer, Dog, Mammary, Pyometra, Tamoxifen

Introduction

Tumours of the mammary gland are the most common tumours in intact female dogs (Tavares,

2010). About 35% to 50% of canine mammary tumours are malignant with tendencies to

metastasize to regional lymph nodes and/or the lungs (Karayannopoulou & Lafioniatis, 2016). The biological behaviour of canine mammary tumours resembles that of humans. Adjuvant chemotherapy, commonly used for the management of human mammary cancer, is often used in dogs as well, and one such adjuvant chemotherapeutic agents is tamoxifen. It is a non-steroidal, anti-estrogenic agent categorized as one of the selective estrogen receptor modulators (Tavares, 2010). It has a complex mechanism of action which includes anti-estrogenic activity in the breast and estrogenic effects in other tissues, including the endometrium (Sobczyńska-Rak & Brodzki, 2014). Tamoxifen has been reported to result in a spectrum of uterine abnormalities such as benign alterations in endometrial polyps, endometrial hyperplasia, cystic endometrial atrophy, adenomyosis, and uterine fibroid growth as well as malignant transformation into endometrial carcinoma and uterine sarcoma (Tavares, 2010).

Uterine pathology has been associated with tamoxifen in dogs (Tran *et al.*, 2014), although the prevalence of such adverse reactions is very low, and most reports are related to experimental administration of the drug (Tavares, 2010). This report presents a case of cystic endometrial hyperplasia-pyometra complex six weeks after administration of oral tamoxifen as adjuvant chemotherapy in a 4-year-old intact nulliparous Boerboel bitch with mammary adenocarcinoma.

Case Management

Case history

A 4-year-old nulliparous Boerboel bitch was presented at the Veterinary Teaching Hospital, Federal University of Agriculture, Abeokuta, with a lump affecting the right cranial lumbar mammary gland. The dog had been treated regularly with Medroxyprogesterone acetate (Depo-Provera®) as a contraceptive. Cytology of the fine needle aspirate from the lump was suggestive of simple mammary adenocarcinoma, while the thoracic radiography was normal. A mastectomy was performed to remove the affected mammary gland. The resected lump was submitted for histopathology, and mammary adenocarcinoma was confirmed. In addition to mastectomy, the bitch was treated with oral administration of tamoxifen (10mg daily) for six weeks as adjunct chemotherapy. Two weeks after the completion of the tamoxifen therapy, the owner reported that the bitch was lethargic, with moderate inappetence and purulent vaginal discharge.

At presentation, the dog was alert with a pink mucous membrane. Rectal temperature (39.8°C) was elevated, while the heart rate (82 beats/min) and respiratory rate (22 cycles/min) were within the normal range. There was copious purulent vaginal discharge. An abdominal ultrasound performed with a portable ultrasound machine (Kaixin KX 2000®, Xuzhou, China), revealed cystic endometrial hyperplasia (Plate I). Thus, a diagnosis of cystic endometrial hyperplasia-pyometra was made. Blood was obtained from the cephalic vein for the determination of complete blood counts, while a sterile swab was inserted high into the vagina to obtain a sample for bacterial culture and sensitivity test.

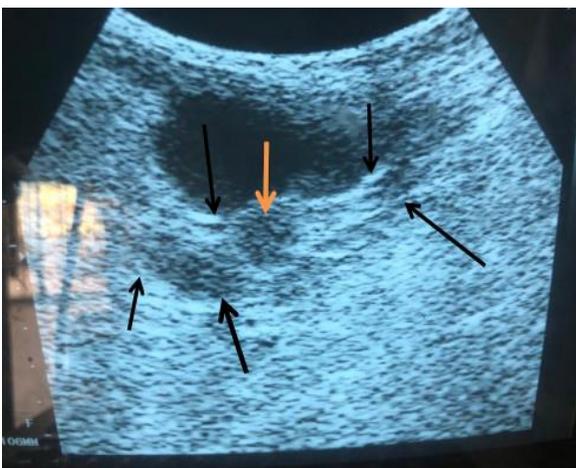


Plate I: Per-cutaneous abdominal ultrasound of a 4-year-old intact Boerboel bitch showing the uterus (Black arrows) with cystic endometrial hyperplasia (Orange arrows)



Plate II: Intra-operative picture of the exteriorized uterus of a 4-year-old nulliparous Boerboel bitch with cystic endometrial hyperplasia pyometra

The complete blood counts showed moderate neutrophilic (absolute neutrophil count = $19.5 \times 10^3/L$) leukocytosis (total leukocyte count = $24.9 \times 10^3/L$), while other parameters were normal. The results of the bacterial culture showed moderate growth of *Staphylococcus aureus*, which was sensitive to Ciprofloxacin, Ofloxacin, Sparfloxacin and Gentamycin. The bitch was thereafter treated with 400µg of Misoprostol (Cytotec®, Pfizer Global Pharmaceuticals, Ikeja, Nigeria) and 500mg of Ciprofloxacin (Ciprotab®, Wockhardt Limited, India) twice daily for two weeks. In addition, 200µg of Misoprostol was administered orally while the other 200µg was inserted intravaginally. However, after two weeks of treatment, the condition of the bitch did not improve significantly as the dogs' appetite was still poor, and the purulent vaginal discharge persisted. Thus, a decision to perform an ovariohysterectomy was made to prevent the uterine infection from spreading to the peritoneal region.

Management

The bitch ventral abdomen was prepared aseptically. The dog was premedicated with 5% tramadol (Tramadol®, Gland Pharma, India), which was administered intramuscularly at the rate of 4mg/kg. About one hour after, a combination of 0.04mg/kg of atropine sulphate (Atocan®, Sishui Xierkang Pharma, China) and 0.5mg/kg of 2% Xylazine Hydrochloride (Xylased, Bioveta, Ivanovice, Czech Republic) mixed in the same syringe was administered intramuscularly for premedication. Immediately the dog became drowsy; venous access was secured at the cephalic vein using a size 21 gauge scalp vein needle, and anaesthesia was then induced with 4mg/kg intravenous injection of propofol (Hyprovan 200®, Celon Laboratories PVT Limited, Telangana, India). The same propofol dissolved in Lactated Ringer's solution and administered at a constant infusion rate of 0.12mg/kg/min was used to maintain anaesthesia. After anaesthesia induction, the dog was positioned in dorsal recumbency, and a ventral midline incision was made. After careful dissection of the subcutaneous tissue, the *linea alba* was located, and a stab incision was made on it. The incision was lengthened using a pair of myo-scissors to gain access into the abdominal cavity. The uterus was located and exteriorized (Plate II) and traced from the uterine bifurcation to the ovarian ligament. The round ligament was gently snapped, and three artery forceps placed between it and each of the ovary. Ligatures were then placed between the artery forceps using size 2 braided Polyglactin 910 (Vioryl,

Anhui Kangning Limited, China). The ovary was then resected off. The same procedure was repeated for the second ovary. Thereafter, the uterine arteries on both side of the uterine body along with the uterus were ligated at the junction between the uterus and the cervix using size 2 braided Polyglactin 910. The uterus was then resected from the cervix, while the broad ligament was resected off using a diathermy instrument to free the uterus and the ovaries. Once the ovaries and the uterus had been removed, the artery forceps were removed and haemorrhages were controlled.

The abdominal incision was then closed in three layers. The *linea alba* was closed with a simple continuous suture pattern using size 2 braided Polyglactin 910 (Vicryl, Anhui Kangning Limited, China). The subcutaneous layer was closed with a subcuticular pattern using size 2 Polyglactin 910 (Vicryl, Anhui Kangning Limited, China), while the skin was closed with a horizontal mattress suture pattern using size two nylon monofilament (Agary Limited, China). Following recovery, 4mg/kg of tramadol injection was administered intramuscularly, while 100mg of tramadol capsule was administered orally for five days post-surgery. In addition, the bitch was treated with intramuscular injections of Enrofloxacin and Amoxicillin for seven days. Both the appetite and temperament of the bitch improved the following ovariohysterectomy gradually. At the same time, vagina discharge stopped four days after surgery.

Discussion

The incidence of mammary cancer continues to increase worldwide, both in humans and companion animals (Pastora *et al.*, 2018). Approximately 35% to 50% of these tumours are malignant with the tendency to metastasize. An increase in the diagnoses of malignant mammary tumours in the bitch is probably linked to the increased exposure to oncogenic substances such as pyrethroids, an important environmental pollutant commonly used as an acaricide. Tumours of the mammary gland are most common in intact bitches as the protective role of early ovariohysterectomy on the development of mammary tumours has been reported (Pastora *et al.*, 2018). Although several histologic types of malignant mammary tumours have been reported in dogs, simple carcinoma form is the commonest reported type of canine mammary tumours. The dog in this report was a 4-year-old s nulliparous dog diagnosed with simple mammary adenocarcinoma. The exact cause of the early development of the tumour in this dog was unknown but may be associated with the

repeated use of medroxyprogesterone acetate (Depo-Provera®) as a contraceptive. Depo-Provera® has been reported to increase the risk of breast cancer in women younger than 45 years of age by 1.5 to 1.65-fold (Li *et al.*, 2012), although such records do not exist for dogs.

Pyometra is a common, potentially life-threatening condition characterized by the accumulation of purulent material within the uterus resulting in both local and systemic symptoms. It is caused by uterine exposure to progesterone during canine dioestrus. Progesterone induces changes in the uterus, which prepare a suitable environment for early embryo development, including endometrial proliferation, increased uterine glandular secretions and decreased myometrial contractions, as well as a relaxation in normal uterine cellular immune (Gibson *et al.*, 2013). This may lead to the development of cystic endometrial hyperplasia, which has been shown to predispose to the development of pyometra. Factors associated with the occurrence of pyometra include administration of long-lasting progestational compounds to delay or suppress estrus, administration of estrogen to mismated bitches and post-insemination and post-copulation infections (Romagnoli, 2017). Although the bitch in this report was previously treated with Depo-Provera® as a contraceptive, the dog did not show any signs associated with pyometra, such as vaginal discharges or depression at the time it was presented for mastectomy. This makes it difficult to associate the development of the pyometra after mastectomy in the bitch to the previous administration of Depo-Provera®. Hence, the reason for inferring that the sudden development of pyometra in the bitch post-mastectomy might be associated with the use of tamoxifen.

Tamoxifen citrate is a selective inhibitor of oestrogen receptors that exerts a potent anti-oestrogen effect on the mammary gland. Previous studies have shown that dogs treated with Tamoxifen developed complications such as pyometra, vulvar swelling and pseudo-gestational behaviour. It has been shown that female dogs exposed to Tamoxifen develop endometrial cell proliferation due to the agonist stimulation of uterine oestrogen receptors (Tavares, 2010). The number of oestrogen receptors increases due to hormonal stimulation with consequent endometrial hyperplasia and an increased number of progesterone receptors. As the number of receptors is increased, leukocyte recruitment to the uterus is reduced, and uterine shrinkage is impaired. This process promotes the reduction of uterine immune

defences and facilitates ascending bacterial infections, mainly caused by *Escherichia coli* resulting in pyometra (Gibson *et al.*, 2013). However, the bacterium isolated from the vagina of this bitch was *Staphylococcus aureus*. The development of pyometra in this bitch post administration of tamoxifen as adjunct chemotherapy further strengthens the need to conduct further evaluation of the safety of the drug as adjunct chemotherapy in dogs.

Ovariohysterectomy is the traditional therapy for canine pyometra. The main advantage of ovariohysterectomy over medical management is that it is both curative and preventive for the recurrence of pyometra. However, the surgical management by ovariohysterectomy is associated with the risk of anaesthesia and renders the bitch sterile. Thus, medical management is usually explored when the owner of the bitch wants to preserve the fertility of the dog. Several medical treatments have been proposed to treat both open and closed cervix pyometra in dogs. Prostaglandins and antiprogestins are the standard treatments for post-oestrus metritis/pyometra in the bitch (Fieni *et al.*, 2014). Luteolytic and uterotonic properties of prostaglandin F2 alpha (PGF2α) have been employed to treat pyometra with repeated doses (Fieni *et al.*, 2014). The most effective medical treatment with minor side effects is the repeated administration of aglepristone with or without the additional treatment with low doses of prostaglandins. Aglepristone is a progesterone receptor antagonist. Aglepristone competitively binds progesterone receptors and decreases intrauterine progesterone concentration (Fieni *et al.*, 2014).

Misoprostol, a type E prostaglandin (PGE), is gradually replacing PGF2α in the management of canine pyometra because it is available in an oral preparation, which can be dispensed to the owner of the dog (Romagnoli, 2017). It is characterized by strong uterine contraction resulting in the evacuation of uterine content. However, it lacks a luteolytic effect. Although misoprostol has been reported to be effective in the management of canine pyometra, the use of the drug in this bitch did not improve the condition of the dog. This may be due to the lack of luteolytic effect by misoprostol as well as the agonist stimulation of the uterine estrogen receptors. Owing to lack of response from medical management and the risk of ascending infection from the uterus into the peritoneal cavity, an ovariohysterectomy was performed.

In conclusion, the use of hormonal therapy to regulate estrus in dogs can predispose to the risk of the development of complications. Although Tamoxifen is routinely used as adjuvant chemotherapy to reduce the risk of recurrence of canine mammary tumours, more work is required to evaluate its safety in intact bitches owing to the risk of development of cystic endometrial hyperplasia-pyometra.

Conflict of interest

The authors declare that there is no conflict of interest.

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