Pyometra in a Bitch Following Placement of a Deslorelin Implant

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ABSTRACT

Cystic endometrial hyperplasia-pyometra complex is a common disease of adult female dogs, causing the accumulation of purulent material within the uterine lumen of intact bitches and typically occurring during or immediately following a period of progesterone dominance. Clinical signs include malodorous, sanguineous to mucopurulent vaginal discharge when the cervix is open ("open pyometra") and systemic illness with no discharge when the cervix is closed ("closed pyometra"). Ovariohysterectomy is the treatment of choice for pyometra; however, combined hormonal and antimicrobial medical treatment is optional when preservation of fertility is desired. The use of gonadotrophin releasing hormone (GnRH) agonists, such as deslorelin acetate, for reversible prevention of estrous cycles has not been found to be a risk factor for pyometra, nor has the use of progestins. In this case report we describe an occurrence of pyometra in a bitch with low progesterone levels and no predisposing factors, after placement of a deslorelin implant and concurrent treatment with progestins. Pyometra in this case was suspected to occur due to a preexisting subclinical uterine pathology primed by progestin treatment. A thorough physical examination, as well as a complete blood count, hormonal panels, ultrasonography and uterine vaginal or urine cultures, are best performed before placing deslorelin implants in bitches, and at regular intervals as long as the implant is assumed to be active.

Key Words: deslorelin acetate, female dog, pyometra, aglepristone, progesterone

INTRODUCTION

Cystic endometrial hyperplasia-pyometra complex, by definition, is the accumulation of purulent material within the uterine lumen of intact bitches, typically occurring during or immediately following a period of progesterone dominance (1, 2). Pyometra is a common disease of adult intact female dogs (3). The mean age of diagnosis is 6-8 years, with a range of 4 to 18 years (4). Age- and breed-related differences in the occurrence of the disease indicate that some breeds are more prone to its development compared to others, and that age and familial predisposition may be present (5).

Clinical signs of pyometra depend on the condition of the cervix. With open-cervix pyometra the most common clinical finding is a malodorous, sanguineous to mucopurulent vaginal discharge. In contrast, bitches with closed-cervix pyometra are generally very ill at presentation, with no evidence of vulvar discharge, with affected bitches often dehydrated, septicemic, toxemic, and in shock (1). Surgical ovariohysterectomy is the primary and preferred method of treatment in all pyometra cases, unless preservation of fertility is desired (6). Medical treatment with compounds that remove the effects of progesterone, promote expulsion of uterine debris, and dilate the cervix, such as Aglepristone (Alizin®, Virbac, Carros, France), in combination with antimicrobials, is optional in some pyometra cases to preserve fertility. The probability of recurrence of

the disease after medical treatment varies between 10-40% (5).

Reversible prevention of estrous cycles in female dogs allows for planned pregnancies at the appropriate time in the animal's lifespan or at the owners' convenience. Controlling estrous to avoid interference with performance or training is also a desirable reason, for treatment, as well as for prevention of disease. Continuous administration of GnRH agonists desensitizes gonadotrophs of the hypophyseal-pituitary-gonadal (HPG) axis, and ovulation is uniformly prevented, forming the practical basis for their use in contraception (7). However, when these compounds are administered to anestrous bitches, there is a short initial stimulation of the HPG axis, described as a "flare-up" period, manifested as an estrous response before the axis is completely suppressed. This immediate effect of GnRH agonists is highly undesirable, and short term administration of progestins suppresses this action without producing any local or systemic side effects (8).

This report describes a case of pyometra in a bitch after administration of a deslorelin implant during anestrus, in conjunction with short term treatment with the progestin megestrol acetate (MGA).

CASE HISTORY

A 2.5 year-old intact Alaskan Malamute bitch, was presented for assessment of purulent vaginal discharge. The reproductive history revealed that her first and second estrous cycles occurred at 18 and 21 months of age, respectively. The bitch was bred on her second estrous cycle, and delivered 8 pups. The pups were either stillborn or died within 48 hours *post partum* of unknown causes. The bitch was treated with antimicrobials for 14 days following whelping and tested negative for Canine Brucellosis 30 days later, using a Rapid Slide Agglutination Test (D-TEC CBmSynbiotics Corporation, Kansas City, MO, USA).

Five months *post partum* a deslorelin acetate implant (Suprelorin® 4.7 mg, Virbac, Carros, France) was implanted subcutaneously, in compliance with the owners' request. The bitch received oral progestin tablets, in the form of MGA (Medisca, Montreal, Canada. compounded by Vetmarket Ltd., Petach Tikva, Israel) for 14 days, from the day of implantation. Thirty days post implant placement, according to the owners, the bitch began displaying overt signs of estrous and was accidentally bred by the stud dog on the premise a few days later. Clinical examination two days post-mating revealed no external clinical signs of estrous. Vaginoscopy revealed a pale vaginal mucosa. On cytological examination large numbers of round vaginal cells, as well as neutrophils with abundant intra- and extracellular rods were found. Based on these findings, a diagnosis of vaginitis was determined. Pure *Streptococcus dysgalactiae* was isolated from the vaginal culture, and the bitch was treated with antimicrobials for 21 days (Amoxicillin clavulinic acid 20 mg/kg twice daily)(Smithkline Becham, Brandford, UK). One month post-administration of antimicrobials the bitch was reported to have a serosanguineal vaginal discharge resembling a regular estrous discharge. The bitch as transferred to a boarding kennel in order to prevent an accidental mating.

Ten days later, malodorous purulent/bloody vaginal discharge in copious amounts was present. Estrous and vaginitis were suspected by a second veterinarian. No treatment was prescribed at that time. On presentation, the bitch was quiet, alert and responsive with a moderate amount of purulent vaginal discharge. Her hydration status was normal with a body temperature of 38.6°C. Transabdominal ultrasonography revealed marked distension of the uterine body, with a diameter of 4.5 cm, and both left and right uterine horns with diameters of 2.3 cm and 2.6 cm, respectively. Hypoechoic fluid, suggestive of pyometra, mucometra, hydrometra or hemometra was observed. Bacteriology results from the vaginal discharge revealed a pure culture of *Echerichia coli*. Serum progesterone results using chemiluminescent immunoassay were 0.35 ηg/ml. (Immulite 2000 Immunoassay Analyzer, Diagnostic Products Corporation (Madison), Los Angeles, California, USA). The bitch was treated with Estrumate (Cloprostenol Sodium, Merck Animal Health, NJ, USA), a synthetic α2-prostaglandin (PGF2α) at a dose of 1 μg/kg IM for 30 days, combined with antimicrobial treatment based on vaginal culture sensitivity results (Amoxicillin clavulinic acid 20 mg/kg or 750 mg twice daily for 14 days (Smithkline Becham, Brandford, UK)). Hospitalization for 24 hours was required as a result of moderate side effects which included trembling, vomiting and diarrhea. Daily ultrasound examination was performed for the first two weeks. One week after commencement of treatment a moderate improvement was noted on ultrasound examination consistent with a reduction in intraluminal fluid content. Aglepristone (Alizin®, Virbac, Carros,

France, 10 mg/kg SQ), was administered and repeated 24 hours later and 3 and 10 days after the initial treatment. Prostaglandin treatment was continued for another 7 days, at which time an abdominal ultrasound showed further improvement and reduction in the dimensions of the uterine body and horns. Prostaglandin treatment was continued for another two weeks, at which time transabdominal ultrasonography revealed complete resolution with absence of intraluminal fluid. The left and right uterine horns measured 10 mm and 8 mm in diameter, respectively. Antimicrobial treatment was continued for a total of 8 weeks.

Ultrasonographic evaluation of the reproductive system after cessation of antimicrobial therapy resulted in complete recovery. There was no evidence of intra-luminal fluid and the uterine horns measured less than 10mm in diameter. Similar results were obtained 4 months later and vaginal culture revealed absence of pathogens.

DISCUSSION

The healthy uterus is capable of eliminating bacterial contaminants without the development of uterine pathologies, however this ability varies depending on the stage of the estrous cycle (5).

Pyometra is mainly diagnosed in diestrus, and is believed to have both hormonal and bacterial components, however, the etiology and pathogenesis are still not completely understood. (5) Estrogen and progesterone levels are not abnormally elevated in most pyometra cases hence different values, or proportions of hormone receptors are thought to be responsible of an exaggerated response to "normal" levels (9). A study investigating the diseased uterine environment of the bitch showed that progesterone levels in diestrus and early anestrus are the main uterine regulators for both progesterone and estrogen receptors, but that in bitches suffering from cystic endometrial hyperplasia and pyometra, the uterus is more sensitive to high levels of progesterone (9). During diestrus, progesterone dominance stimulates uterine gland secretion and prevents luteolysis by suppressing prostaglandin activity (1,4). Progesterone also suppresses the response of the immune system to pathogens as well as uterine contractions. In the bitch, bacterial colonization is possible under these conditions. Bacterial contamination of the uterus likely occurs prior to diestrus when the cervix is open and in cases of cystic endometrial hyperplasia bacteria cannot be cleared prior to the luteal phase. These opportunistic organisms are able to colonize the uterus and proliferate within the uterine environment (1). *Eschrichia coli* (*E. coli*) bacteria, a natural inhabitant of the vaginal flora, has been isolated from about 70% of pyometra cases (2, 5).

Gonadotrophin Releasing Hormone (GnRH) agonists are peptides similar to GnRH, however, they are modified at sites of the enzymatic degradation of GnRH (7). This modification increases their resistance to peptidases and enhances receptor binding affinity. Substitution of a bulky hydrophobic D amino acid at position 6 and the replacement of the C-terminal glycinamide residue by an ethylamide group produces compounds of up to 200 times more potent than naturally occurring GnRH in releasing gonadotropins (7). Deslorelin implant, a GnRH agonist, is a D-TRP-Pro-des-Gly-GnRH slow release analogue, administered by way of a subcutaneous controlled release device, with a duration activity of at least 6 months or greater than 12 months, depending on the formulation used. When administered to control reproduction in companion animals it results in overstimulation of the pituitary gland, down-regulation of GnRH receptors, suppression of the gonadotropin luteinizing hormone (LH) and follicle stimulating hormone (FSH), and a decreased progesterone secretion. (10). The mechanism of action, suppression of the HPG axis, is well known, and has been successfully employed in the prevention of cyclic activity of many species (11). Deslorelin administered to anestrous bitches has been found to cause proestrous and estrous signs within 7-10 days before the period of estrous suppression. (5) This acute effect was not detected in bitches treated during diestrus i.e. plasma progesterone concentration >5ηg/ml (12), or in bitches pretreated with progestin (8, 12).

MGA is a good choice for progestin administration, as it terminates proestrus, blocks ovulation, and prevents *corpus luteum* formation. A study showed no local or systemic side effects when MGA is administered short term in conjunction with Deslorelin (8). A commonly used protocol consists of MGA given orally (2.2 mg/kg *per os* daily) for 8 to 14 days, starting 4 days prior to deslorelin treatment. When using this protocol estrous rate is expected to appear in 10% of the deslorelin implanted bitches (8). In the case described, it was assumed that the implant was administered in anestrus, as the time elapsed from whelping to the implantation was 5 months. However, it cannot be ruled out that the bitch may have experienced a silent or an unobserved estrus shortly

after whelping and was actually in diestrus when deslorelin implant was administered. If so, progestin administration may have facilitated the precipitation of pyometra as it promotes cervical closure, suppresses uterine motility, stimulates endometrial development and secretion (possibly leading to cystic endometrial hyperplasia), suppresses the uterine immune response to pathogens, as well as priming progesterone and estrogen receptor response.

The Alaskan Malamute has not been included in any study to date in the list of breeds at risk for developing pyometra (3,13); risk factors that have been investigated and validated statistically include low parity –with nuliparous bitches at greatest risk – and increasing age (3,4,13,14). It is therefore of note that the bitch in this case, with no known predisposition i.e. either nulliparous or aged does not belong to any 'at risk' breed, nonetheless developed pyometra. It is well described in the literature that short-term administration of progestagens at therapeutic doses does not induce pyometra or other undesirable side effects in bitches (13, 14). In addition, serum progesterone levels at time of diagnosis were low i.e. below 1 ηg/ml. It is possible that the bitch suffered from a cystic uterine environment that was primed by progestin treatment, together with pathogenic remnants from a previous suppurative infection postpartum, predisposing to the development of pyometra as in this case.

Based on the presented information regarding the possible side effects of the combined deslorelin and progestin treatment it can be concluded that a thorough physical examination, as well as complete blood count, biochemistry panel, hormonal panels (e.g. serum progesterone), uterine ultrasonography and vaginal or urine cultures are best performed before administering deslorelin implants to bitches. These procedures should be instituted at regular intervals as long as the implant is assumed to be active and/or until the next estrous cycle occurs. It is advisable that these implants are placed where they can be removed should it be required, such as at the umbilical scar or vulvar skin.

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