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Cystic endometrial hyperplasia with pyometra complex and it's surgical management in canine

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Abstract

Pyometra is a condition characterized by accumulation of pus within the uterus. Canine Pyometra can be categorized based on status of cervix as open cervix or closed cervix. Pyometra is a potentially life threatening condition associated with cystic endometrial hyperplasia. Cystic endometrial hyperplasia is an abnormal uterine response that develops during diestrus when there is high or prolonged ovarian production of progesterone. Bacterial origin can be traced by most common presence of *E. Coli* along with endotoxins. Pyometra can be diagnosed by Physical examination, clinical examination, radiography and USG. For treatment of pyometra combination therapy of aglepristone and cloprostenol over 15 days has been reported safe and effective with few side effects. Other than medicinal therapy surgical treatment ovariectomy is the preferred treatment for pyometra.

Keywords: Pyometra, radiography, USG, hormone, ovariectomy

Introduction

Canine pyometra is a common reproductive syndrome of intact, sexually mature bitches during met/diestrous stage with various clinical as well as pathological signs specific to reproductive system along with systemic signs (Fransson, 2003) [5].

Pyometra is a condition characterized by uterine inflammation with accumulation of purulent semisolid material within the uterus. In the bitch and queen, pyometra is a hormonally mediated diestrus disorder. The disease results from bacterial infecting an endometrium that has undergone pathologic changes exaggerated by progesterone stimulation. Pyometra is sometimes referred to as cystic endometrial hyperplasia pyometra complex.

Canine Pyometra can be categorized based on status of cervix as open-cervix or closed-cervix; however, closed type is more serious condition, which needs surgical intervention so as to prevent concomitant sepsis and fatality (Smith, 2006) [10].

Pyometra is a potentially life-threatening condition associated with cystic endometrial hyperplasia.

Pathophysiology

In dogs, the diestrus period of a normal, non-gravid bitch lasts approximately 70 days. The uterus is influenced by progesterone produced by ovarian corpora lutea. The plasma progesterone concentration in the anestrus bitch is less than 0.5 ng/ml. For approximately 2 months following ovulation the plasma progesterone concentration is increased. During this period progesterone promotes the growth and secretory activity of the endometrial glands and reduces myometrial activity. Thus, allowing accumulation of uterine glandular secretions. These secretions provide an excellent environment for bacterial growth. Bacterial growth is further enhanced by inhibition of the leukocyte response to infection in the progesterone-primed uterus.

Cystic endometrial hyperplasia is an abnormal uterine response that develops during diestrus (luteal phase of cycle) when there is high or prolonged ovarian production of progesterone or exogenously administered progesterone. Excessive progesterone influence or an exaggerated progesterone response causes the uterine glandular tissue to become cystic, edematous, thickened, and infiltrated by lymphocytes and plasma cells. Endometrial thickening is caused by an increase in the size and number of endometrial glands, which may show secretory activity. Endometrial gland secretion results in an accumulation of thin or viscid fluid within the lumen of the uterus with cystic endometrial hyperplasia.

Uterine drainage is hindered by progesterone inhibition of myometrial contractility. This abnormal uterine environment allows bacterial colonization to cause pyometra. Administration of estrogen increases the risk of pyometra during diestrus. Estrogen, by itself, is not usually associated with the development of cystic endometrial hyperplasia or pyometra. However, estrogens increase the number of uterine progesterone receptors on the uterus, which may increase the risk of developing pyometra after estrogens are administered. Feline pyometra is less frequent than canine pyometra because development of luteal tissue requires copulation or artificially induced ovulation.

Etiology

Bacterial origin can be traced by most common presence of *E. Coli* along with endotoxins (Hageman, 2004; Bondade *et al.*, 2010). *E. Coli* has an affinity for the endometrium and myometrium. Bacterial virulence is associated with the serotype, presence of K antigen and cytotoxin necrotizing factor. However, several other pathogenic bacteria are also identified as causative agent, *i.e.*, *Klebsiella Spp.*, Streptococci, Staphylococci, anaerobic bacteria, Pseudomonads (Dhaliwal *et al.*, 1998) [2]. Several workers narrated that susceptibility of host and pathogenic bacteria along with progesterone appears to be an important component leading to disease condition (Krekeler *et al.*, 2012a; 2012b) [8, 9].

Clinical Pathology

Metabolic clinic-pathologic abnormalities may occur. The most common hemogram findings are neutrophilia with a left shift, monocytosis, and white blood cell toxicity. The total white blood cell count is usually increased in the bitch with closed-cervix pyometra, often exceeding 30,000 cells per μl and may be as high as 100000 to 200000 cells per μl . An absolute neutrophilia with variable degrees of cellular immaturity may progress, with subsequent infection and septicemia, to a degenerative left shift with toxic neutrophils. Many dogs with open-cervix pyometra do not exhibit evidence of the overwhelming infection seen in closed-cervix

pyometra. Approximately 50 percent of bitches with open-cervix pyometra that the authors have examined have had total white blood cell counts within the high normal range or only mildly elevated (fewer than 25,000 cells per μl) prior to initiation of any therapy.

A mild normocytic, normochromic, non-regenerative anemia or non-regenerative microcytic hypochromic anemia may occur (packed cell volume 28-35 ml/dl). Common biochemical abnormalities include hyperproteinemia (total protein of 7.5 to 10.0 gm/dl) and hyperglobulinemia and azotemia result from dehydration and chronic antigenic stimulation of the dog's immune system. Serum urea nitrogen concentration may be increased if dehydration is present. Hyponatremia and hyperkalemia may occur with severe vomiting or diarrhea, mimicking hypoadrenocorticism. Occasionally, alanine aminotransferase and alkaline phosphatase concentrations are mild to moderately increased from hepato-cellular damage caused by septicemia and/or diminished hepatic circulation and cellular hypoxia in the dehydrated bitch. Hyperglycemia or hypoglycemia may be associated with concurrent diabetes or sepsis. Urinalysis may reveal isosthenuria, proteinuria, and/or bacteriuria

Urine specific gravity is variable. Early in the disease process, the urine specific gravity may be greater than 1.030. With secondary bacterial infection, especially with *E. Coli*, toxemia develops that may interfere with the resorption of sodium and chloride in the loop of Henle.

Urinary tract infections may be suspected if pyuria, hematuria and proteinuria are found in the urinalysis. However, urine obtained by a midstream collection may be dramatically altered if a vaginal discharge is present. We do not recommend cystocentesis on dogs with suspected or known pyometra. There is a risk of puncturing the infected uterus, with subsequent leakage of uterine contents into the abdomen, causing peritonitis. Open pyometras (and some closed pyometras) have a septic vaginal exudate (*i.e.*, neutrophils, many degenerates, with bacteria). Aerobic and anaerobic bacterial culture and susceptibility are essential for selection of appropriate antibiotics.

Table 1: Serum and blood parameters with their significance in differentiating disease diagnosis

Parameters	Healthy dog values	Values in Pyometra affected bitch	Significance
Haemoglobin (g/dl)	11.9-18.9	11.9	Within the normal range
PCV (%)	35-57	37	Within the normal range
TLC ($\times 10^3/\mu\text{l}$)	5.0-14.1	6.9	Within the normal range
Neutrophils (%)	58-85	95	Relative Neutrophilia
Lymphocytes (%)	8-21	4	Within the normal range
Monocytes (%)	2-10	01	Within the normal range
AST (IU/L)	5-55	29.9	Within the normal range
ALT (IU/L)	10/109	59.6	Within the normal range
Urea (mg/dl)	8-28	21.2	Within the normal range
Creatinine (mg/dl)	0.1-2	0.67	Within the normal range

Diagnosis

Signalment and History

Historically, pyometra is a disorder of middle-aged bitches (8 to 10 years old), developing after years of repetitive progesterone stimulation of the uterus. The risk of an intact bitch developing pyometra before 10 years of age is nearly 25%. Breed susceptibility is also observed in this condition with high risk include Rottweiler, Saint Bernard, Chow chow, Golden Retriever, Miniature Schnauzer, Irish Terrier,

Airedale Terrier, Cavalier King Charles Spaniel, Rough Collie, and Bernese Mountain dog (Smith, 2006) [10]. Domestic shorthair and Siamese cats are affected more commonly than other breeds. Breed susceptibility strongly indicates the contribution of genotype towards increase or decrease risk of disease (Jitpean *et al.*, 2012) [7]. Pyometra generally occurs in older (1.8 to 14 years, median 7.9 years) intact bitches and queens (Hagman *et al.*, 2011) [6]; however, it may occur in younger animals that have been given

exogenous estrogen (dogs) or progestins (cats). Nulliparous bitches are at moderately greater risk for pyometra than are primiparous and multiparous bitches, but this finding is not consistent across at-risk breeds (Hagman *et al.*, 2011) [6].

The signs reported by the owner depend on the patency of the cervix. A bitch with open-cervix pyometra has a sanguineous to mucopurulent discharge from vulva. The discharge is usually first noticed 4-8 weeks after standing heat or as late as 12 -14 weeks after the end of standing heat. Other signs include lethargy, depression, inappetance, polyuria, polydipsia and vomiting. It is also common for bitches with open cervix pyometra to be relatively healthy except for the presence of an abnormal vaginal discharge.

Signs in bitches with closed-cervix pyometra include lethargy, weakness, depression, inappetance, polyuria, polydipsia and vomiting. Occasionally, an owner will have noticed a discharge from the vulva prior to the onset of other signs, which lasts only a few days. Vomiting and anorexia in conjunction with polyuria will cause progressively dehydration, shock, coma and eventually death. The severity of illness at the time of presentation is dependent on the ability of owner to recognize the problem.

Physical Examination

Physical examinations include depression, dehydration. A purulent blood-tinged vaginal discharge may occur if the cervix is open. Uterine enlargement may be difficult to detect by palpation, especially if the uterus is draining much of its contents or if the uterus is enlarged but flaccid. Abdominal radiography can be used to confirm uterine enlargement. The rectal temperature can be elevated, normal, or even subnormal and when present, is associated with uterine inflammation and secondary bacterial infection as well as septicemia or bacteremia. With septicemia or bacteremia animal may be in shock. Overzealous palpation should be avoided to prevent rupture of the uterine wall. A palpable uterus is always considered an abnormal finding in the non-pregnant bitch or queen in diestrus.

Radiography

It is important to rule out pregnancy. Radiographic visualization of the uterus at other times is abnormal. Abdominal radiography should be assessed in a bitch with suspected pyometra to confirm the diagnosis. With pyometra, a fluid-dense tubular structure should be seen in the ventral and caudal abdomen, displacing loops of intestine dorsally and cranially (Fig.1,2). Open pyometra or uterine rupture may cause enough drainage so that the uterus is not radiographically detected. In addition to confirming the diagnosis of pyometra, radiographs may provide important information regarding the medical status of a bitch. Two major concerns in a dog with pyometra are the presence or absence of peritonitis from a uterine rupture and retained fetal tissue from a previous pregnancy. Abdominal compression may be of value using a belly band or wooden spoon to displace the intestines away from the uterus. This procedure may enhance radiographic contrast and often allows improved visualization of the uterus but should be performed with caution if the uterus is significantly distended because it may induce rupture.

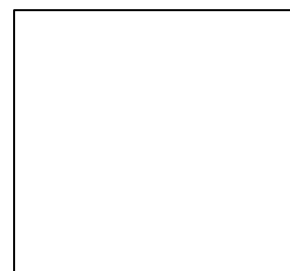


Fig 1: Fluid-dense tubular structure



Fig 2: Enlarged uterus in the caudoventral abdomen

Ultrasonography

Ultrasonography has greatly enhanced the clinician's ability to document pyometra, especially when abdominal radiographs are inconclusive. Ultrasound allows determination of fetal viability, uterine size, the thickness of the uterine wall and irregularities and the presence of fluid accumulation within the uterus (Fig.3). Pyometra, hydrometra, mucometra, or hematometra may appear similar ultrasonographically and radiographically. However, although mucometra and hydrometra typically are associated with anechoic fluid within the uterine lumen on ultrasound, the fluid associated with pyometra is typically echogenic (Fig.4).

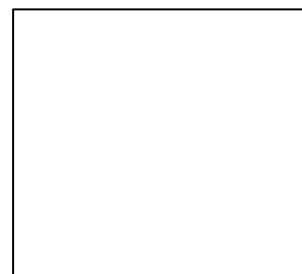


Fig3: Enlarged fluid filled uterus

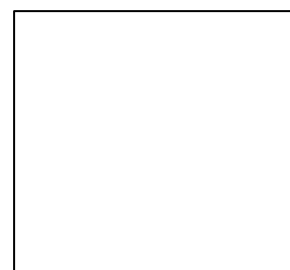


Fig4: Fluid within the lumen of uterus is mildly echogenic

Differential Diagnosis

Differential diagnoses include mucometra, hydrometra, hematometra, hydrocolpos, pyovagina, pregnancy, metritis, placentitis, uterine torsion, and peritonitis. Because of its high percentage of bandneutrophils, elevated C-reactive protein, elevated alkaline phosphatase, and evidence of clinical illness, pyometra is more likely than mucometra.

Treatment

Medicinal Treatment

Medical therapy utilizing estrogens, androgens, ergot alkaloids, quinine and oxytocin is inconsistent and often unsuccessful. Prostaglandin should be used with caution in bitches with closed-cervix pyometra because of the potential for uterine exudate being expelled into the peritoneal cavity, causing peritonitis. Although estrogens may relax the cervix, their use prior to PGF₂ α therapy is not recommended because of estrogen enhancement of the progesterone effects on the uterus.

Medical therapy is most appropriate for animals with an open pyometra. Prostaglandin, is not approved for use in the bitch, but it is available for use in the cow and the mare. Owners should be informed that the use of PGF₂ α , for treating canine pyometra is experimental.

Multiple protocols have been described to medically address pyometra (Verstegen *et al.*, 2008) [11]. Medical therapy with antibiotics for 2 to 3 weeks and with PGF₂ α or preferably aglepristone (antiprogesterin) combined with cloprostenol

(synthetic prostaglandin) should be considered only for metabolically stable, valuable, breeding animals.

Prostaglandin, has several physiological effects on the female reproductive system, including contraction of the myometrium. This effect results in expulsion of the exudate accumulated in the uterus.

Combination therapy of aglepristone and cloprostenol over 15 days has been reported safe and effective with few side effects (Fieni, 2006) [4]. Alternatively, combination therapy of cabergoline (dopamine agonist) with cloprostenol has also been found to be a safe and efficient treatment for pyometra (Corrada *et al.*, 2006; England *et al.*, 2007) [1, 3]. Including an antilipoplysaccharide to reduce endotoxins may be beneficial.

Short-term side effects (30 to 60 minutes) include panting, salivation, emesis, defecation, urination, mydriasis, nesting, tenesmus, lordosis, vocalization, and intensive grooming. High doses of prostaglandin may cause ataxia, collapse, hypovolemic shock, respiratory distress, or death. Expect pyometra to recur in 20% during subsequent estrus cycles.

Table 2: Doses of drugs used in pyometra

Drugs	Dose rate
PGF ₂ α	0.1 mg/kg SC once on day 1, 0.2 mg/kg SC once on day 2 0.25 mg/kg SC once daily on days 3-7
Aglepristone (Alizine; Virbac, Carros, France)	10 mg/kg SC, days 1, 3, 8, and 15
Cloprostenol (Estrumate, Schering Plough, Argentina)	1 μ g/kg SC q24hr for 7 to 14 days or every 3 rd day
Cabergoline (Galastop; Ceva, France)	5 μ g/kg PO q24hr for 7 to 10 days

Surgical Treatment

Ovariohysterectomy is the preferred treatment for pyometra. Urine output, glucose, and arrhythmias should be monitored preoperatively. Hydration, electrolyte, and acid-base imbalances should be corrected before surgery, if possible (the prognosis is improved when azotemia is corrected before surgery). A broad-spectrum antibiotic effective against *E. Coli* (e.g., cefazolin, cefoxitin, enrofloxacin, and ticarcillin plus clavulanate) should be given intravenously.

Anesthesia

Anesthetic protocols vary greatly depending on patient status. Animals that are systemically ill need to be closely monitored during anesthesia. The anesthesia is achieved by parenteral or inhalation anaesthetic after proper premedication.

Positioning

Position the patient in dorsal recumbency for a ventral midline celiotomy. The entire ventral abdomen should be clipped and prepared for aseptic surgery

Surgical Technique

- A 6-8 cm long incision is made on the midline beginning over the umbilicus and extended caudally.
- Skin, subcutaneous tissue, linea alba, falciform ligament and peritoneum are incised. The incision may be extended in obese animal or in animal having enlarged uterus.
- An ovariotomy hook is introduced towards the left flank into the cavity and uterine horn or broad ligament is hooked and is withdrawn. In case ovariotomy hook is not available, an index finger can be passed to locate uterine horn. Uterus and ovary are recognized and uterine horn is grasped with gauze sponge.

- It is convenient to remove the left ovary, then the right ovary and finally the body of the uterus.
- The ovarian bursa is clamped across by artery forceps. The ovary is grasped between thumb and index finger and withdrawn for ligation.
- The suspensory ligament of the ovary is ruptured by traction or with forceps and ovary is withdrawn from the abdomen and a large opening is made in the broad ligament with fingers or forceps to expose the ovarian attachment with its blood vessels.
- Application of three artery forceps facilitates the ligation procedure for ovarian pedicle. The proximal forceps form a groove for the ligation. The middle forceps serve to hold the stump for ligation and the distal forceps check the haemorrhage from the severed vessels.
- A double ligation with chromic catgut size 1-0 is used to ligate ovarian pedicle. The attachment between the ligation and the ovary is then severed. The severed stump should be checked carefully for haemorrhage before returning it to the abdomen.
- After removing one ovary, the other ovary is located and removed in the similar manner.
- The broad ligament is then severed. Care being taken to avoid the blood vessels near the uterus.
- The body of the uterus is withdrawn from the abdomen. The uterine vessels are ligated on each side and cut. Transfixation double ligation is used to encompass the entire cervix. The uterus is severed just cranial to the ligatures.
- Uterine stump is checked carefully for haemorrhage, if any, and returned into the abdomen. Care should be taken to remove as much uterine body as possible.
- Abdominal incision is closed in the usual manner.



Fig 5: Intraoperative and postoperative images of closed cervix pyometra

Other Technique- Marsupialization

Marsupialization is a technique for treatment of closed chronic pyometra in the bitch. If the animal is toxemic and aged such animal may not bear the stress of ovariohysterectomy as they are animal of poor surgical risk. In such animal Marsupialization is done to treat such closed pyometra cases. This is also a type of surgical treatment which can be performed under sedation and local infiltration of 2% Lignocaine HCl at lower lateral flank area. In this technique a small laparotomy incision is made in flank and uterus is sutured with wound edges and then incised to drain the pus. A tube is kept in place for 3-5 days and when complete drainage of pus occurs tube is removed and is sutured. Then after giving supportive therapy ovariohysterectomy may be performed after 1 or 2 months. This technique minimizes the chances of post anaesthetic mortality in pyometra cases and owner must be well informed about risk. Thus successful surgical management of cases chronic uterine endometrial hyperplasia with pyometra depends upon condition of patient, extent of abdominal distension, duration of suffering and preoperative preparation of animal using fluid therapy, antibiotic and corticosteroid.

Postoperative Care

- Give analgesics as necessary. Meloxicam @ 0.2-0.3 mg/kg IM for 3 days.
- These patients should be monitored closely for 24 to 48 hours for sepsis and shock, dehydration, and electrolyte/acid-base imbalances.
- Severe hypoproteinemia or anemia may require plasma or blood transfusions, respectively.
- Fluid therapy should be continued postoperatively until the animal is eating and drinking normally.
- Given antibiotic injections like Inj. Amoxicillin 300 mg IM or I/V for 5 days.
- Maintenance of antibiotic therapy based on culture and sensitivity results should be continued for 10 to 14 days. Amoxicillin plus Clavulanate (Clavamox) Dogs: 12.5-25 mg/kg PO q12hr.
- Low-dose dopamine or diuretics may be given postoperatively if urine production is reduced.
- Dopamine (low dose) 0.5-3.0 µg/kg/min IV.

- Mannitol 0.25-1 g/kg IV over 15 min.
- Furosemide (Lasix) 2-4 mg/kg IV, PO, SC q8-12hr.
- Evidence of abdominal discomfort, elevated temperature, or pain suggests peritonitis.

Complications

- Septicemia, endotoxemia, peritonitis, and cervical or stump pyometra may occur. Stump pyometra may be associated with residual ovarian tissue.
- Other complications include anorexia, lethargy, anemia, pyrexia, vomiting, icterus, hepatic disease, renal disease, and thromboembolic disease.

Prognosis

- Prognosis following surgery is good if abdominal contamination is avoided, shock and sepsis are controlled, and renal damage reversed by fluid therapy and bacterial antigen elimination.

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