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Association of canine pyometra with systemic inflammatory response syndrome

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Abstract
Pyometra is one of the most common diseases in intact bitches. It is usually accompanied by glomerular and tubular dysfunction leading to renal failure. Present report depicts the involvement of multiple organ system along with pyometra leading to the systemic inflammatory response syndrome. Ovariohysterectomy was performed after stabilizing the animal however the animal died ten days after the surgery due to renal failure. Future perspective includes development of prophylactic measure like the development of a vaccine designed against certain virulent factors of bacteria associated with pyometra can be done for susceptible animals. Hence prompt diagnosis and early treatment schedule that may be parenteral therapy or surgical approach (ovariohysterectomy) would subject the older animal to good prognosis.

Keywords: Pyometra, ovariohysterectomy, systemic inflammatory response syndrome, renal failure

Introduction
Canine pyometra is an infectious and acute or chronic multi systemic reproductive disorder occurring most commonly in diestrus and sometime in anestrus phase [1]. It results in high mortality if left untreated [2]. Pyometra is documented as one of the main cause of death in the bitch [3]. Approximately 25% of intact female dogs suffer from pyometra before 10 years of age [4] however female dogs are predisposed to pyometra after 8 years of age [4, 5]. Various theories are suggested to establish the pathogenesis of pyometra, however the most acceptable theory dictates that due to principal hormonal imbalance or abnormal response of animal to normal concentrations of estrogens and progesterone during luteal phase affects the growth rate of epithelial cells in the uterus and helps in bacterial adherence, establishment and progression [6, 7]. Estrogen stimulates the uterine cell growth and increases endometrial vascularization which in turn raises the uterine sensibility and its response to progesterone. A high level of progesterone leads to endometrial proliferation and increased glandular secretions and suppresses myometrial contractions and inhibits leukocyte infiltration in the uterus [8], hence causing cervical closure [9, 10].

Predominantly in almost 70% of the cases, *Escherichia coli* are isolated in most (62-90%) pyometra cases [11, 12, 13]. Prevalence of this high proportion of *E. coli* might be due to the fact that they are natural microflora/ opportunistic microbes present in the vaginal passage and they move to the uterus during proestrus and oestrus phase [14]. After gaining entrance into the uterine tissue, *E. coli* colonize and proliferate in the epithelial lining uterus. Certain pathogenic strains of *E. coli* are having virulence factors that have the ability to bind specific receptors in the endometrium of canines [15].

Progression of uterine infection causes a severe endotoxemia and ultimately leads to SIRS i.e. systemic inflammatory response syndrome [7]. The syndrome is characterized by serious infection and inflammatory response that cause production and release of inflammatory mediators which affect the body systemically [16, 17]. There is no gold standard for the diagnosis of SIRS, but parameters have been derived from the human literature for dogs and cats. The presence of three or more of the following clinical signs is highly suggestive of SIRS in dogs: tachypnea (RR>40 breaths per minute or), tachycardia (HR >120 beats per minute), leukocytosis or leukopenia (WBC>18,000/µl or 5-10%), and fever or hypothermia (T>104˚F or <100.4˚F) [33]. Occurrence of SIRS with pyometra has previously been identified in over 50% of bitches suffering from the disease; however it has been associated with long term medication and grave prognosis [7, 11].

Many treatment schedule has been designed for treating pyometra such as using antibiotics alone [18, 19] or using the parenteral route [20-22] or intravaginal [23] administration of prostaglandin F2α (PGF). So far ovariohysterectomy is the best prophylactic and therapeutic method for pyometra in canines [24]. The present case depicts the involvement of multiple organ system along with pyometra leading to systemic inflammatory response syndrome in pomeranian bitch. Ovariohyterectomy was performed after stabilizing the animal however the animal died ten days after the surgery due to renal failure.

Case history and Clinical findings

A 12 years old female Pomeranian was presented in GADVSAU clinics with the history of sanguineous purulent vaginal discharge from last one month. Animal was anorectic and dull upon presentation. Animal was showing signs of abdominal discomfort, frequent urination (polyuria), increased water intake (polydipsia), vomiting and lethargy. This was in accordance with the classical signs noted by Fransson [25] in case of canine pyometra. Physiological parameters were recorded and they show variation from the normal as depicted in table 1. This show the infection in the uterus has progressed to the systemic route and has led to the development of the systemic inflammatory response syndrome as discussed in the previous section. Vaginal swab sample was taken in sterilized phosphate buffer saline and were cultured for bacterial isolation. revealed the presence of *E. coli* in the pus.

Due to low hemoglobin the animal was kept on supportive therapy for three days and after that blood transfusion was done. Major matching of the donor blood with the recipient was done. Before blood transfusion, parenteral administration of Inj. 2 ml dexamethasone (Dexona ; Zydus Cadila, Ahmedabad) and 2 ml phenramine maleate (Avil; Sanofi Aventis, Goa) was done to avoid a hypersensitive response. Approximately 350 ml i.e 1 unit of blood is transfused using blood transfusion CPDA bag (Kruuse CPDA bag; Jørgen Kruuse A/S, Denmark) containing 49 ml CPDA. Antibiotics ceftriaxone and metronidazole were given along this. Initially transfusion rate was slow 0.25 ml/ kg for 30 minutes to identify an incompatibility among donor and recipient blood. After that transfusion rate was increased to 2-10 ml/kg/hour and alter increased to 10-20 ml/kg/hour. The whole transfusion process took about 3 hours [26]. One day after blood transfusion, complete blood count was done to ascertain the animals response to blood transfusion. Hemoglobin levels were elevated but creatinine and BUN levels became quite high indicating acute renal failure and making animal unfit for ovariohysterectomy. Keeping in view the condition of the animal and consent of owner, emergency ovariohysterectomy was performed. In dogs and cats, complete OVH performed through a ventral median celiotomy is the preferred surgical treatment for diseases affecting the uterus, including pyometra [27]. Post-operative medication was done using ringer lactate 200 ml for 2 days, amoxicillin (20mg/kg b.w.: AMC forte; Carus Laboratories Pvt. Ltd., Karnal), enrofloxacin (5mg/kg b.wt.: Floxidin; MSD, Pune), meloxicam @ 1ml (Melonex; Intas, Ahmedabad) and multivitamin were given for 5 days.

Laboratory Findings

Hematological and biochemical examinations were done. Hematological findings depict severe anemia with leukemoid response. It indicates the presence of immature cells such as myeloblats or red blood cells with nuclei in the peripheral blood, suggestive of physiological response to stress or infection (Table 1). Leukocytosis, with neutrophilia and left shift in the differential leukocyte count along with toxic changes in the neutrophils is also observed. Band cells in the blood smear was examined in the count.

Vaginal swab culture revealed presence of *E. coli* bacteria. Biochemical profiling depicts renal dysfunction in at its initial phases when the animal was presented. Blood urea nitrogen and creatinine levels were at their highest and the level starts declining to its normal range after the surgery (Table 1). Nephropathy is commonly observed in canine pyometra along with raised level of Alkaline Phosphatase (ALKP) and Alanine aminotransferase (ALT) pre operatively however the level starts declining following surgery.

Uterine diameter was also recorded using ultrasonography and it is around 2.94 cm with lumen diameter around 1.34 cm. It is clearly suggestive of pyometra with increased thickening of endometrium due to inflammatory changes.

Post-operative follow up

Animal recovered speedily after the surgery. Response of the animal was good after surgery. After 10 days of surgery owner noticed limb edema in the hind limbs of an animal and recumbency from five days. Animal was anorectic from 3 days and had not passed faces since surgery. Water intake was normal and urination was normal. Hematological examination revealed severe anemia and neutrophilic leukocytosis while blood biochemical analysis revealed normal BUN and creatinine levels. Animal was given DNS 5% 150 ml, Amoxycillin 250 mg (AMC forte; Carus Laboratories Pvt Ltd, Karnal), Belamyl 2ml (Multivitamins; Zydus Cadila, Ahmedabad), Metronidazole 30 ml (Metrogyl; J B Chemicals, Mumbai), Ranitidine 1.5 ml (Aciloc; Cadila Pharmaceuticals Ltd, Ahmedabad) and Frusemide (Lasix; Sanofi Aventis, Goa) 1 ml for 3 days. Eventually the animal died 9 days after surgery. Post-operative complications are suggestive of renal failure.

Table 1: Physiological and hematological parameters of pyometra affected bitch

Parameter	On 1st day	On the day of operation	After 10 days of operation
Hematological parameters			
Hb (gram %)	3.7	7.8	4.6
TLC (10^5/ cu mm)	1.19	1.05	0.45
TEC (10^6/ cu mm)	1.83	3.58	2.15
PCV (%)	11.4	18	13.2
Platelet (*10^3)	472	325	538
Neutrophils (%)	98	97	92
Lymphocytes (%)	02	03	08
Biochemical parameters			
AST(U/L)	21	65	85
ALT(U/L)	40	91	97
BUN (mg/dL)	73	140	40
Creatinine (mg/dL)	2.4	15.5	1.2
Physiological parameters			
Heart rate (bpm)	92	110	140
Respiration rate (per minute)	88	40	72
Rectal temperature (ºF)	100	101.5	100.9
CMM	Pale	Slightly pink	Slightly pink
Dehydration	+++	++	++

Discussion

Identification and diagnosis is upfront in cases presented with classical signs, but may be challenging in the cases where vaginal discharge is not there (closed pyometra) and when the signalment and blood picture is unclear. Hematological and biochemical values show alteration form the normal values in case of pyometra [7, 25, 28]. Generally leukocytosis in present with any kind general body of infection but leucopenia is associated with grave prognosis. Chronicity of the infection is reflected as normocytic, normochromic anaemia, decreased erythropoiesis, lack of available iron and loss of RBC's in the uterus [29]. Overall, the most common signs of disease, present in > 50% of the bitches, included vaginal discharge, anorexia, depression, polydipsia, and polyuria (Table 1) reflects the systemic involvement of the disease in the majority of bitches [24, 30, 31]. In canine pyometra, low haemoglobin (Hb) along with low packed cell volume (PCV) value and low total erythrocyte count (TEC) was suggestive of normocytic normochromic anemia [32]. However finding the anemic patient with mild normocytic, normochromic and non-regenerative anemia is most common [33] which ultimately advances to a microcytic, hypochromic anemia, if there is simultaneous blood loss.

Kidney dysfunction is commonly observed during canine pyometra and can be associated with elevated levels of alkaline phosphatase and Alanine aminotransferase (ALT) [25, 28]. Though antibiotic therapy can be attempted, but ovariohysterectomy is the treatment of choice to prevent uterine rupture and septicemia where the animal is systemically ill, both in case of open or closed pyometra [10].

In older animal, systemic involvement along with pyometra in the current case predisposed the animal to grave prognosis whether ovariohysterectomy is done or not. Current findings of renal failure are in accordance with Maddens *et al*. [28] where he reported renal failure in 2 of 25 (8%) dogs with *Escherichia coli* pyometra. Hence prompt diagnosis and early treatment schedule that may be parenteral therapy or surgical approach (ovariohysterectomy) would subject the older animal to good prognosis.

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