Global Veterinaria 13 (1): 60-67, 2014
ISSN 1992-6197

DOI: 10.5829/idosi.gv.2014.13.01.84160

Ultrasonography and Pathological Evaluation of Cystic Endometrial Hyperplasia Pyometra Complex in Bitches and Queens with Related Ovarian Alterations

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Abstract: Cystic endometrial hyperplasia - pyometra complex (CEHP) is a common female genital disorder encountered in bitches and queens, the etiopathogenesis of the condition is a complex one. This study aimed to investigate the role of ultrasonography and pathological examination as tools for diagnosis of the condition in addition to analyze the correlation between the development of the condition and related ovarian changes in bitch and queen. During the period from January 2010 to May 2013, 12 bitches and 36 queens of different breeds and ages (7 months up to 13 years) were examined clinically and by ultrasonography for CEHP then ovariohysterectomy was performed in positive cases. Tissue specimens from ovaries, fallopian tubes and uteri were collected for pathological examination. Obtained results indicated that higher incidence of CEHP was recorded in bitches and queens over six years old and the affection was more frequent during spring season. Griffon and Persian breeds were the most common affected breeds in bitches and queens respectively. Clinically, affected animals suffered from inappetence, depression, polydipsia, lethargy and abdominal distension with or without fever and vaginal discharge. Ultrasonographical examination revealed fluid filled uterus with variable wall thickness and proliferative changes. Gross examination revealed distension of uterine horns by capacious amount of pus with thickening and exaggerated nodularity. Microscopically, intense suppurative inflammatory reaction involving endometrial mucosa with marked cystic dilatation and hyperplastic proliferation of endometrial glands were observed. Moreover, variable ovarian alterations accompanied the development of CEHP. In conclusion, CEHP is a common genital affection in bitches and queens with seasonal and breed variation. Ultrasonography is a good diagnostic tool. Contraceptive pills administration and ovarian cysts are incriminated in the pathogenesis of such affection.

Key words: Pyometra · Cystic Endometrial Hyperplasia · Ultrasonography · Ovariohysterectomy · Uterine Nodularity · Dog · Cat

INTRODUCTION

Pyometra is a common female genital affection in bitches and queens. Pyometra is defined as the endometritis/cystic endometrial hyperplasia/pyometra complex (CEH/P) [1]. It was noted that pyometra is a uterine affection of intact, sexually mature bitches and queens [2, 3]. Cystic endometrial hyperplasia (CEH) in the bitch and queen may result in pyometra, haematometra, or hydrometra and it is difficult to differentiate between these uterine affections [4]. Cystic lesions in the uteri of bitches and queens aroused from the uterine serosa, myometrium or endometrium and include serosal inclusion cysts, adenomyosis, endometrial polyps, cystic remnants of mesonephric ducts and cysts associated with endometrial hyperplasia (both cystic glands and "pseudo-placentational" hyperplasia) [5]. Previous studies clarified that bitches

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that developed the condition were at an age ranging from four months to 16 years [6].

CEH is a common histological finding in multiparous queens older than three years and in other queens older than five years without relationship to the number of parturitions [7]. On the other hand, the average age of queens suffering pyometra was seven years [8]. CEH was more prevalent in small breeds than large ones, while the condition was less observed in queens presumably due to its induced ovulatory nature [9]. Bernese Mountain dog, Rottweiler, rough haired Collie, Cavalier King Charles Spaniel and Golden Retriever breeds were listed as predisposed ones [10].

The affection often results in subtle changes in the early stages; therefore, diagnosis is often possible late in the disease process [3, 11]. It is worthy to mention that diagnosis of pyometra (chronic purulent endometritis post-oestrum) in bitches could be clinically difficult to be differentiated from those with cystic endometrial hyperplasia (CEH) in combination with sterile seromucous fluid in the uterine lumen (hydrometra) or mucometra depending on the water content of the fluid [12]. Bitches and queens with pyometra may present either with a vaginal discharge (open-cervix pyometra) or without a vaginal discharge (closed-cervix pyometra). Closed-cervix pyometra requires rapid intervention to prevent overwhelming sepsis and the potential of patient death due to pyometra is not widely recognized by clinicians or pathologists [5]. Pyometra is at risk of a suddenly developing endotoxic shock that may be fatal while bitches and queens with non-infected uteri (CEH/ mucometra) are not regarded as potential emergencies [13].

Clinically, a bitch might be presented with inappetence, depression, polydipsia, polyuria, vomiting, lethargy and abdominal distension, with or without vaginal discharge [3, 14]. Ultrasonographic examination could be useful and reliable tool for diagnosis of cystic endometrial hyperplasia [15]. A fluid filled organ with variable wall thickness and proliferative changes could be visualized [15, 16].

The characteristic uterine pathology includes inflammatory and hyperplastic reaction involving the endometrial mucosa with cystic dilatation of endometrial glands; the inflammatory reaction may extend to involve completely uterine wall [17]. The etiopathogenesis is complex, hormonal disorders and bacterial infections are the underlying causes of this complex. Cystic endometrial hyperplasia often predisposes the dog to pyometra [18, 19] due to over growth of normal vaginal flora that enters the uterus at distress phase [20]. The most commonly isolated bacteria in such cases is *E.coli* and in some cases *Staphylococci*, *Streptococci* and *Pseudomonas Aeruginosa* [1].

The treatment of choice for any older, systemically ill bitch and queen, or one with closed-cervix pyometra, is total ovariohysterectomy [2, 3]. Attempted medical management of bitches with closed-cervix pyometra might result in uterine torsion, severe hemorrhage or uterine rupture, with seepage of uterine contents into the abdomen [21, 22]. So, medical management of closed-cervix pyometra is contraindicated due to the potential for life-threatening complications [23]. Some authors tried to treat the case via injection of Prostaglandin F2 alpha (PGF2a) subcutaneously every 12 hours at a dose of 250 mg/ kg for 3-5 days until the uterus approaches its normal size [2, 24]. Cases those require longer therapy treatment, or show a recurrence of fluid in the uterus, indicate a poor prognosis for prostaglandin treatment success. Recovered bitches that fail to conceive or complete a subsequent cycle without being bred can have a high incidence of recurrence of pyometra [2, 24].

The present work aims to find out the breed, age and seasonal incidence of cystic endometrial hyperplasia-pyometra complex (CEH/P) in bitches and queens. In addition, it aims to present the ultrasonography and pathological uterine picture and accompanying related ovarian alterations with an attempt to assume a correlation between the uterine pathology, ovarian alterations and management of pyometra in bitches and queens.

MATERIALS AND METHODS

The material used in the present study comprised a total number of 48 bitches and queens with pyometra (12 bitches and 36 queens). They were of different breeds and their age ranged between 7 months to13 years. Those cases were admitted to the surgery clinic at Faculty of Veterinary Medicine, Cairo University, Military Veterinary Hospital and three private veterinary clinics at Giza and Cairo provinces during the period from January 2010 to May 2013. A full case history, animal description and clinical examination findings were reported for each animal and complete physical and abdominal examination were carried out.

Ultrasonographical examination was carried out using a real time B-mode scanner (Aquila Vet C E 0344,

Piemedical, Esaote Europe B.V.; Maastricht, the Netherlands) equipped with dual frequency 5 / 7.5 MHz curved array probe. For cats and small breed dogs, 7.5 MHz transducer was used and 5 MHz transducer for large breed dogs [25].

After tentative diagnosis of pyometra, ovariohysterectomy was performed according to the procedure described by Johnston *et al* [8]. Intra-muscular Cefotaxime sodium at a dose of 10 mg kg^{-1} and Diclofenac sodium at a dose of 1.1 mg kg^{-1} once/day for 5 days after surgery were given to control the post operative pain [26]. Removed organs from affected bitches and queens were subjected to gross examination. Then specimens from ovaries and uterus were collected and fixed in 10% buffered neutral formalin. Such tissues were routinely processed, dehydrated in ascending concentration of ethanol, cleared in xylene, embedded in paraffin and sectioned at 2-4 μm thickness. Prepared slides were stained by hematoxylin and eosin [27].

RESULTS

As shown in Table 1, the age of affected bitches and queens ranged from7 months to 13 years. The highest incidence of pyometra was recorded in bitches and queens more than six years old (Table 1). The number of affected bitches breeds were Griffon (3), German shepherd (2), Pitbull (2), Mix (2), Boxer (1), Rottweiler (1) and Yorkshire terrier (1). Regarding the affected cat breeds, they were Persian (20), Mix (9) and Siamese (7). Regarding seasonal distribution, the highest incidence of pyometra in bitches and queens was recorded during spring followed by autumn, winter and the least incidence was in summer (Table 2).

The obtained results showed that the highest incidence of the pyometra was reported in bitches and queens given contraceptives (Table 3).

The most common recorded symptoms of pyometra included inappetence, depression, polydipsia, lethargy, abdominal distension and fever and or vaginal discharge in some cases. Abdominal examination revealed distension and pain. Ultrasonographical examination revealed fluid filled organ with variable uterine wall thickness and proliferative changes (Figure 1).

Uterine Pathological Lesions of Cystic Endometrial Hyperplasia Pyometra Complex: Lesions in uterine wall were illustrated in Figures [2 (a-f) & 3 (a-c)]. Gross examination revealed enlarged uterus with distension of both uterine horns by capacious amount of pus. Cut sections showed exaggerated nodularity of the uterine mucosa, while microscopical examination revealed diffuse infiltration of uterine lumen by neutrophils mixed with cell debris and focal sloughing of endometrial epithelium. The endometrial stroma showed diffuse infiltration by lymphocytes, macrophages and plasma associated with interstitial edema.

The endometrial epithelium showed hyperplastic proliferation. In addition, the endometrial glands showed cystic dilatation and hyperplasia of its epithelial lining that contained mass collection of neutrophils in its lumen. In severe cases of pyometra, the inflammatory reaction extended to the underlying myometrium that showed vacuolation and necrosis of smooth muscle cell and congestion of blood vessels with mononuclear cell infiltration, adenomyosis of endometrial glands with associated stroma were observed in myometrium in two bitches with CEHPC. Moreover, typical cystic endometrial hyperplasia had been detected in four bitches that were characterized grossly by enlarged uterus and on cross section, the endometrial mucosa showed diffuse thickening and exaggerated nodularity. Microscopically the lesion was characterized by marked cystic dilatation of endometrial glands with mononuclear cell infiltration involving the endometrial stroma and no detectable suppurative inflammatory reaction in the endometrial mucosa. Concerning fallopian tube no lesions were detected in the collected samples.

Table 1: Age distribution of pyometra in the present study

	Cases	
Age Groups (Years)	Bitches	Queens
< 2	0	2
2 – 3	0	11
3 – 4	0	2
4 – 5	3	5
5 – 6	4	6
> 6	5	10
Total	12	36

Table 2: Seasonal distribution of pyometra in the present study

	Total	
Season	Number	%
Winter (December, January, February)	11	22.9 %
Spring (March, April, May)	16	33.3 %
Summer (June, July, August)	10	20.9 %
Autumn (September, October, November)	11	22.9 %
Total	48	100 %

Table 3: Relation between contraceptive and pyometra

Species	Pyometracases that were given contraceptive	Pyometra cases that were not given contraceptive
Bitches	10	2
Queens	27	9
Total	37	11

Fig. 1: Ultasongram of CEH/P in 4.5-year-old Persian queen showing fluid filled uterus with variable uterine wall thickness and proliferative changes

Ovarian Histological Alterations of the Ovaries Associated with Endometrial Hyperplasia Pyometra Complex: The ovarian changes that associated the development of CEHPC were illustrated in Figures (3d-f), most cases showed persistent corpus luteum on ovaries. In seven bitches and four queens, the ovaries contained follicular cysts that were unilateral and characterized grossly by presence of single to multiple thin walled straw colored fluid filled cysts. Microscopically the cyst was lined by non-luteinized granulosa cells internally, theca cells externally and the lumen was distended by eosinophilic fluid. In one queen, CEHPC showed cystic reti ovarii that was characterized microscopically by presence of numerous cysts that were lined by flattened epithelium. Other cases showed normal histological ovarian structures.

DISCUSSION

Cystic endometrial hyperplasia pyometra complex (CEHPC) is a purulent inflammatory and hyperplastic condition of the uterus affecting adult bitches and queens. It is one of the most common uterine affections occurring in adult bitches as nearly one fourth of all bitches before reaching ten years of age are affected [28].

Concerning the age of the affected bitches and queens, the results of the current study showed that it ranged from 7 months to 13 years. In spite the wide range of age of affected pets, the highest incidence of pyometra was recorded in bitches and queens of more than six years old. Similar results were previously mentioned [6, 7]. However, one fourth of cystic endometrial hyperplasia pyometra complex cases were bitches more than 4 years

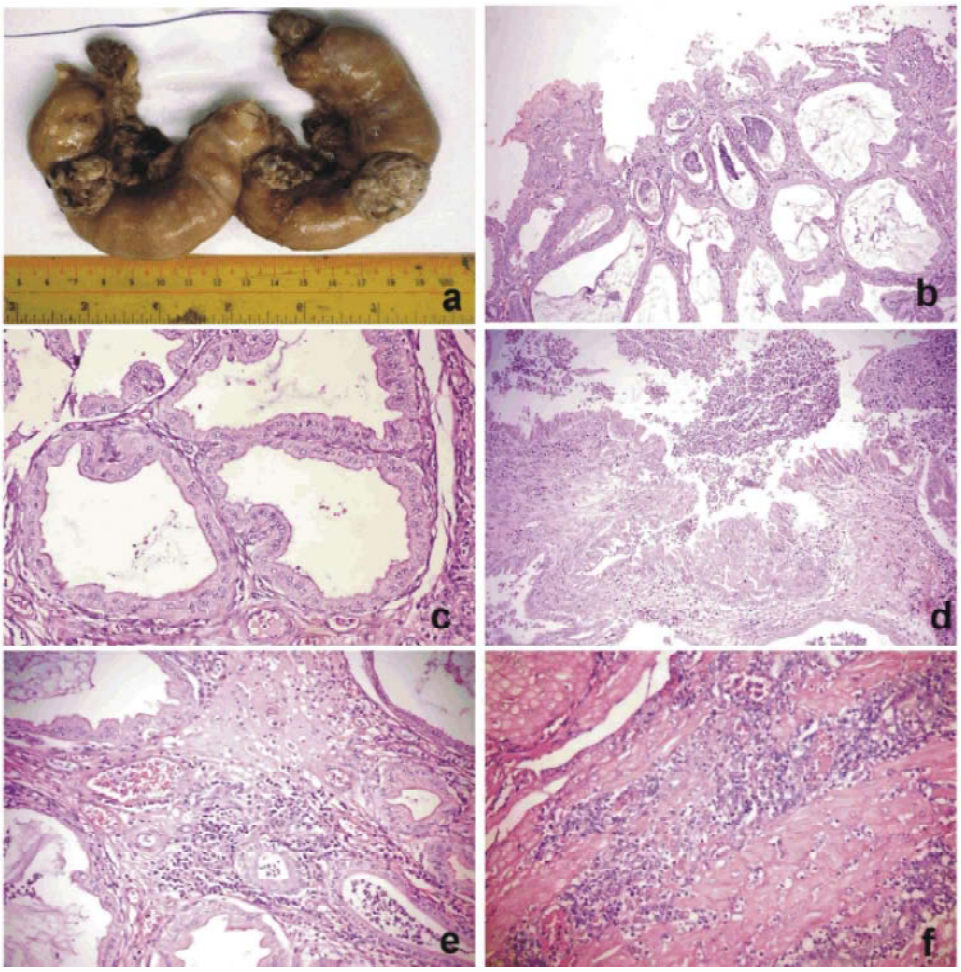

Fig. 2: (a) Uterus of a bitch showing enlargement and distension with pus also thickening and nodularity of endometrial mucosa. (b) Endometrium of a bitch showing marked cystic dilatation and hyperplastic proliferation of endometrial glands (H&E X100). (c) Higher magnification of the hyperplastic endometrial glands showing that they are lined by tall columnar cells with vesicular nuclei (H&E X400). (d) Endometrium of a bitch showing intense aggregation of neutrophils mixed with cell debris covering the endometrial mucosal epithelium that shows hyperplasia (H&E X200). (e) Endometrium of bitch showing interstitial edema with mononuclear cells infiltration in periglandular area with dilatation of blood capillaries (H&E X400). (f) Endometrium of a queen showing intense inflammatory cells infiltrating the myometrium that showing vacuolization of smooth muscle cells associated with dilated blood capillaries (H&E X400)

old and less than ten years old [28]. Whereas the mean age of the cases in that study was 9.4 ±0.4 years at the time of clinical signs. Other studies recorded an increased incidence of pyometra in nulliparous bitches and in bitches less than 4 years of age [29]. Regarding the affected breeds, in the present study, Griffon and Persian breeds were the most commonly affected breeds among dogs and cats respectively. However, previous studies mentioned extra other breeds [10].

As regard seasonal distribution of CEHPC, the highest incidence of pyometra in bitches and queens was recorded in spring, without logic or accurate explanation of such result. However, this might be related to the fact that those pets are diseasonal-estrous animals. Moreover, the incidence of pyometra was higher in bitches and queens that were given contraceptive. As only eleven cases out of forty-eight cases affected with pyometra were not given contraceptive, indicating the most possible magnified role of contraceptive administration in induction of pyometra. On the other hand, CEH–Pyometra complex can affect both bitches undergoing contraceptive treatment or not [30].

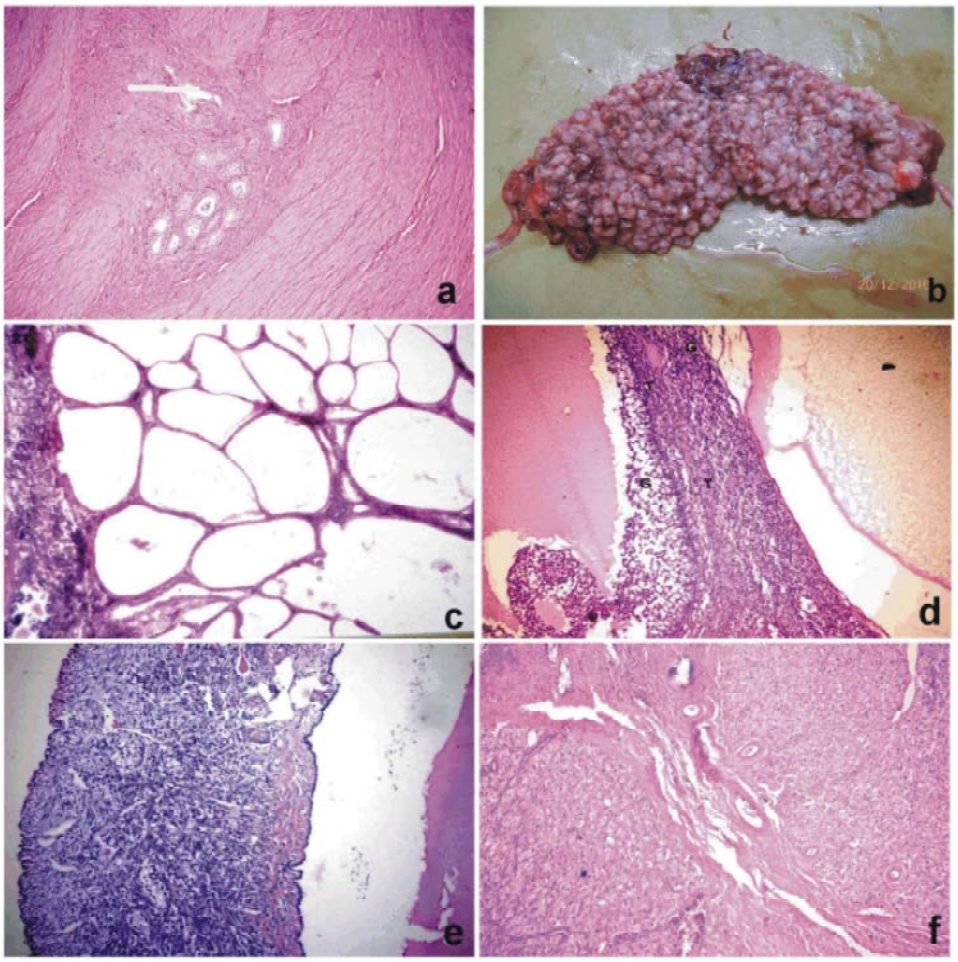

Fig. 3: (a) Myometrium of a bitch showing adenomyosis, notice the presence of endometrial glands in between muscle bundles that supported by well- developed stroma (H&E X100). (b)Uterus of a bitch showing exaggerated nodularity on endometrial mucosa. (c) Endometrium of a bitch showing marked cystic dilatation of endometrial glands with mononuclear cells infiltration into the underlying stroma (H&E X200). (d) Ovary of a bitch showing large follicular cyst filled with eosinophilic follicular fluid and lined internally by partially luteinized granulosa cells (G) and externally by theca cells (T). (H&EX100). (e) Ovary of queen with cystic rete ovarii compressing the ovarian stroma (H&E X100). (f) Ovary of a bitch showing two large persistent corpus luteum occupying most of ovarian tissue (H&E X100)

In the present study, the most common clinical symptoms associated with pyometra were inappetence, with or without fever, depression, polydipsia, lethargy, with or without vaginal discharge and abdominal distension. Moreover, abdominal examination revealed distension and pain. Similar signs were recorded before [3, 12]. Ultrasonography is a helpful tool for diagnosis and treatment of various surgical affections of genital tract [31]. In the present study, pyometra had characteristic ultrasonographic features as fluid filled uterus with variable wall thickness and proliferative changes. Similar findings were also mentioned [15, 16, 32].

The obtained results proved that Ovariohysterectomy as a surgical interference is still the ideal approach for dealing with pyometra. A result that agrees with those previously mentioned [2, 3, 15, 16]. The present histopathological studies revealed that cystic endometrial hyperplasia pyometra complex is characterized by increased thickness of the uterine wall with nodularity of endometrial mucosa associated with uterine intra luminal aggregation of purulent exudates. The lesion is characterized microscopically by three main histological alterations. The first is the presence of suppurative inflammatory reaction involving endometrial mucosa that

extended in some cases into the underlying uterine layers. The second alteration is the marked cystic dilatation and hyperplasia of endometrial glands. The last one is the progestational proliferation of the endometrial glandular epithelium that showed vacuolated cytoplasm and individual pyknotic nuclei. More or less similar findings were recorded before [15]. The correlation between the cystic endometrial hyperplasia pyometra complex in bitches and queens and the ovarian histopathological alterations were studied. The ovarian alterations included follicular cysts, cyst retie ovarie and persistent corpus luteum. Elevated estrogen level from follicular cysts or contraceptive pills was incriminated in endometrial over proliferation and elongating the period at which the uterine cervix remains open. Other authors discussed the correlation between pyometra and follicular cyst [33, 34].

The fore-mentioned results together with those regarding the role of contraceptive pills administration prove the multifactorial etiopathogenesis of the CEHPC. Such results are agrees with those suggested before [17]. Moreover, estrogen and progesterone receptors were modified in cystic endometrial hyperplasia [35]. Similarly, Agudelo [2] described the persistent corpus luteum that was correlated with CEHPC in the present study. He also found that about 40-70% of the pyometra cases were associated with corpora lutea. In the meantime, pyometra in queens was diagnosed during the follicular phase [36], which is influenced by estrogen besides progesterone. Johnston *et al.* [37] explained the role of progesterone in induction of CEHPC, as it exerted its action on canine uterus through decreasing its local immune reactivity, promoting the secretion of endometrial glands, decreasing uterine motility and finally closure of uterine cervix.

CONCLUSION

Cystic endometrial hyperplasia - pyometra complex (CEHP) is a common genital affection in bitches and queens and of breed and seasonal incidence. Ultrasonography is an accurate diagnostic tool. Contraceptive pills administration and ovarian cysts are incriminated in the development of the affection. It is accompanied by severe various pathological uterine alterations that are observed and considered characteristics for CEHP.

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