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Literature Review

Canine pyometra – an update and revision of diagnostic terminology

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Abstract

Pyometra is frequently diagnosed in female dogs, and it is characterized by endometrial inflammation, accumulation of purulent exudate within the lumen, and bacterial infection. In the dog, pyometra affects more often aged nulliparous bitches during the luteal phase. Pathogenesis of pyometra is multifactorial and progesterone seems to be a key factor. Cystic endometrial hyperplasia has been described as a predisposing condition for canine pyometra. However, a recent study demonstrated that cystic endometrial hyperplasia is not significantly associated with naturally occurring pyometra, whereas there is a significant association of this condition with pseudoplacentational endometrial hyperplasia. The aim of this review is to provide an update on canine pyometra, with focus on its association with uterine hyperplasic lesions, which supports a proposal for adoption of more adequate diagnostic terminology.

Key words: female dog; endometritis; pseudoplacentational endometrial hyperplasia; reproductive pathology.

Introduction

Pyometra is a condition characterized by uterine inflammation with accumulation of purulent exudate within the uterine lumen, associated with bacterial infection that results in systemic illness (12, 24). Pyometra may affect several animal species (1-4, 25, 30, 33, 36, 37). In female dogs, pyometra is a life-threatening disease that affects, more frequently, old nulliparous bitches, during the luteal phase when there are higher of progesterone plasmatic levels (12, 38).

The pathogenesis of pyometra in female dogs is complex, and it is affected by several factors including bacterial infection, neutrophilic activity, uterine motility, and concentration of immunoglobulins (42). Although the pathogenesis of pyometra is not completely understood, it is accepted that pyometra is a disease of the diestrus, and that high progesterone levels are critical for development of infection (8, 12, 43).

Early studies suggested an association of pyometra and cystic endometrial hyperplasia (CEH) so the condition was named "CEH – pyometra complex" (12). However, the concept of "CEH - pyometra complex" has been currently questioned. There is no clear demonstration of a cause and effect relationship between these two pathologic changes, which are both associated with diestrus, and both affects aged bitches. Additionally, the severity of the clinical signs in bitches with pyometra does not correlate with the currently used histological classification (8), which undermines the communication between pathologists and clinicians. Importantly, another common hyperplastic condition that affects the canine endometrium, namely pseudoplacentational endometrial hyperplasia (PEH), has been recently characterized as an endometrial change that also commonly develops during the diestrus (43).

A recent study demonstrated that there is no significant association between CEH and naturally occurring pyometra (39). These findings are in sharp contrast with the

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classical concept that there is a cause and effect relationship between these uterine lesions in bitches (12). Interestingly, a significant association and positive correlation between PEH and pyometra was demonstrated (39). These findings prompted us to revise the concept of "CEH - pyometra complex".

The aim of this review is to provide an update on canine pyometra, with emphasis on the association of pyometra with hyperplastic endometrial changes, which supports a proposal for adoption of more adequate diagnostic terminology.

Clinical and epidemiologic aspects of canine pyometra

Pyometra is a uterine pathologic change that is commonly diagnosed in intact female dogs. Usually, pyometra affects middle-aged to old female dogs, with median age ranging from 6.50 to 9.36 years (12-14, 17, 27). Some studies demonstrated breed predisposition, with higher incidence in Bernese Mountain Dog, Collie, Rottweiler, Cavalier King Charles Spaniel, Golden Retriever, Bullmastiff, and Dogue de Bordeaux (13, 17, 27). These findings suggest that genetic factors may predispose or prevent the development of the disease (13, 17, 27).

Studies carried out in Sweden, involving approximately 200,000 bitches, demonstrated an incidence of pyometra of 2.10% and 1.99% (13, 27). Another study including 165 colony-raised Beagle dogs in Japan, demonstrated an incidence of pyometra of 15.2% (14). In a retrospective study in five hospitals in the United Kingdom, from 2006 to 2011, involving 78,469 dogs, the prevalence of pyometra was 2.2% and the incidences were 1.8% and 2.9%, in 2006 and 2011, respectively (17).

Clinically, uterine fluid accumulation and enlargement of the uterus may be due to mucometra, hydrometra or pyometra. Mucometra and hydrometra are characterized by intrauterine storage of sterile mucous or serous fluid, respectively. The difference between these conditions is the degree of hydration of the fluid (40, 42). Although bitches with hydrometra or mucometra may develop an enlargement of the abdomen, more often there are no clinical signs associated with those conditions (38). However, diagnosing these conditions is important since they may result in sub-fertility or infertility (21).

In contrast to mucometra or hydrometra, pyometra is characterized by an inflammatory component, and it is associated with severe bacterial infection. Consequently, bitches may develop clinical signs that require emergency intervention, especially in cases when the cervix is closed. Therefore, classification of pyometra in open-cervix or close-cervix is clinically relevant. In cases of open-cervix pyometra the purulent uterine exudate is drained through the cervix, resulting in a sanguineous purulent malodorous vulvar discharge that is easily identified. Conversely, in cases of close-cervix pyometra the cervix remains closed and the purulent exudate is retained within the uterus (Fig. 1), which increases the risk of endotoxemic shock and there is even the possibility of uterine rupture. Although bitches with any of these classifications may develop septicemia, in close-cervix pyometra the prognosis is worse, with quickly progressing depression, polyuria, polydipsia, vomiting, and diarrhea (38). In addition, the vulvar discharge in cases of open-cervix pyometra allows the owner to early identify the condition usually resulting in therapeutic intervention before the development of systemic clinical changes.

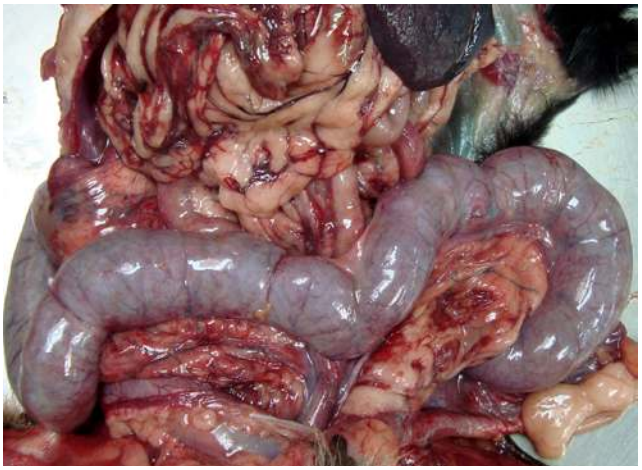

Figure 1. Female dog with pyometra. Abdominal cavity with marked enlargement of the uterus due to accumulation of purulent exudate in a case of close-cervix pyometra.

Several changes in laboratorial parameters may be observed in bitches with pyometra. Leukocytosis with neutrophilia is the most frequent laboratorial finding in cases of pyometra. However, in more severe cases there may be leucopenia due to neutrophil sequester within the uterine lumen. Endotoxic effects on the bone marrow may result in anemia, thrombocytopenia and, consequently, extramedullary hematopoiesis (20). Bitches with pyometra may develop renal lesions, including tubular and glomerular lesions, which may also result in blood or urinary biochemical changes (32).

Pyometra may lead to endotoxemia and systemic inflammatory syndrome (SIRS). Clinical laboratory analysis is a tool for determining the severity of this systemic condition so it is useful for establishing a treatment protocol and prognosis. Serum levels of prostaglandin $F_{2\alpha}$-metabolite and C-reactive protein are increased in bitches with pyometra, especially when pyometra is associated to SIRS (20, 22).

Ultrasonographic examination is a useful technique for diagnosis of uterine lesions in bitches. This technique allows evaluation of uterine integrity, measurement of the uterine wall, and assessment of cysts or luminal distention (6). Uterine intraluminal fluid can be identified ultrasonographically and, usually, there are features that may allow differentiating mucometra, hydrometra, or

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pyometra (38). However, these fluid characteristics are not definitive parameters for the diagnosis. A study with bitches in diestrus indicated that Doppler ultrasonography may further support the diagnosis of pyometra. The uterine artery of bitches with pyometra has higher end diastolic velocity, higher peak systolic velocity, and lower resistance index, compared to bitches with endometrial hyperplasia with or without mucometra, or with a normal diestrus (5).

Stabilization of the general systemic condition of the bitch followed by ovariosalpingohisterectomy still the most recommended treatment for pyometra (24). Postsurgical follow up should include assessment of kidney function and antibiotic therapy for at least one week. When reproductive activity is desirable, conservative medical treatment is a possibility, but there is risk of recurrence (19, 34, 49).

Estrogen treatment has been proposed for relaxing the cervix and promoting uterine contraction. However, it also causes undesirable effects including medullary suppression and vasodilatation that increases absorption of toxins (49). Because of these side effects, estrogen treatment is no longer recommended. Therapeutic protocols usually have some common goals: (i) blocking progesterone effects by promoting luteolysis or blocking progesterone receptors; (ii) drainage of the purulent exudate by relaxing the cervix and inducing uterine contractions with prostaglandins or progesterone receptor antagonists; (iii) prevent bacterial growth with antibiotic therapy; and (iv) favor uterine regeneration, by prolonging the anestrus by using mibolerone, an androgen receptor-agonist (49).

Pathogenesis of canine pyometra

The pathogenesis of canine pyometra is multifactorial so bacterial infection, hormonal stimulus, genetic predisposition, and other uterine lesions all play a role in the development of the disease. However, hormonal stimulus seems to be a key factor for triggering the development of pyometra.

Female dogs are polytocous and have a monoestral non-seasonal estrous cycle with spontaneous ovulations. Importantly, intact bitches are repeatedly exposed to progesterone during the diestrus, which length is independent of pregnancy or matting. The diestrus or luteal phase of estrus cycle persists for 50 to 80 days in non-pregnant bitches and approximately 65 days in pregnant bitches (7). Progesterone induces reduction in myometrial contractility, decreased uterine blood flow, and impairment of neutrophilic migration into the uterus (42). Furthermore, progesterone alters endometrial innate immune response to bacterial infections, inhibiting IFN_Y, TLR4, and TLR2 expression (46, 48). Importantly, pyometra is a disease that develops during the diestrus (8, 12, 39), and the uterus has higher levels of innate immune response to *Escherichia coli* during the estrus when compared to the diestrus (48). Together, these findings support the notion that the development of bacterial infection in cases of pyometra is favored by the effect of progesterone on the uterus.

Lactoferrin, an iron-biding glycoprotein, that plays an important antimicrobial role (50). Lactoferrin expression in canine endometrium is higher during proestrus and estrus compared to the diestrus, but it is increased in cases of pyometra (29). Furthermore, the endometrial surface is covered with mucin, particularly the protein known as Muc1, which protects the endometrium against infection by preventing bacterial adhesion (10, 18). Possibly, reduction of lactoferrin and Muc-1 endometrial expression during the diestrus may predispose to bacterial infections by favoring bacterial adherence to endometrial epithelium and colonization of the uterine environment (26, 29). Although endometrial expression of lactoferrin is increased in cases of pyometra, neutrophils display the most intense immunostaining for lactoferrin, suggesting that this increasing is due to neutrophilic infiltration rather than an actual increase in expression by endometrial cells (29).

Historically, pyometra has been associated with CEH in bitches. An early and highly relevant study that was based on experimental induction of CEH and pyometra in neutered and hormonally-treated bitches supported the hypothesis that pyometra is secondary to CEH, and therefore the condition was named "CEH – pyometra complex" (11). The author also suggested that the complex was associated to high progesterone levels and that previous hyperestrogenism could worsen the condition (12). In this context, a classification including four types of canine pyometra manifestation (types 1 through 4), based on histopathological changes, was proposed.

Although the concept of "CEH – pyometra complex" has been largely accepted by pathologists and clinicians, this concept has been recently questioned. Progesterone levels in bitches with pyometra are not higher than in bitches without uterine lesions during diestrus (24). Furthermore, endometrial hyperplasia and pyometra are conditions that develop during the diestrus, affecting animals of the same age range, suggesting that these changes occur at the same time, but not necessarily that they have a cause and effect relationship (8). Importantly, PEH has been well characterized as an endometrial hyperplastic change that is distinct from CEH, although both develop during the diestrus (43). Indeed, a recent study demonstrated that there is no significant association between CEH and pyometra, whereas pyometra is significantly associated with PEH (39). It is noteworthy that the seminal work by Dow (11, 12) was based on experimentally induced uterine changes, which under a pathogenesis standpoint may not quite be a surrogate of naturally occurring pyometra. Furthermore, prior to the study by Schlafer and Gifford (43), very likely PEH may have been extensively misdiagnosed as CEH, thus supporting the concept of a "CEH – pyometra complex" throughout the years. However, in spite of the fact that a significant association between PEH and pyometra has been

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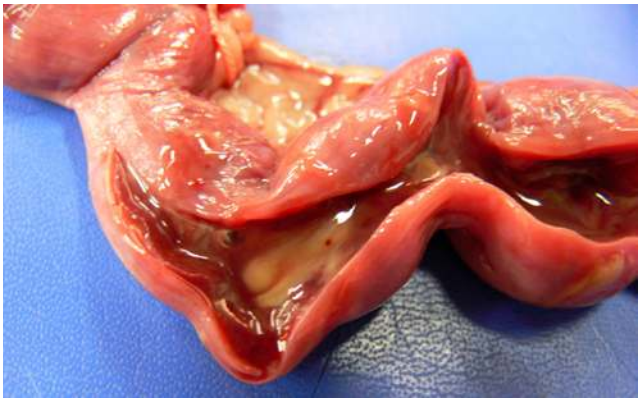

Figure 2. Female dog with pyometra. Moderately enlarged uterus, with small amounts of intraluminal purulent exudates in a case of open-cervis pyometra.

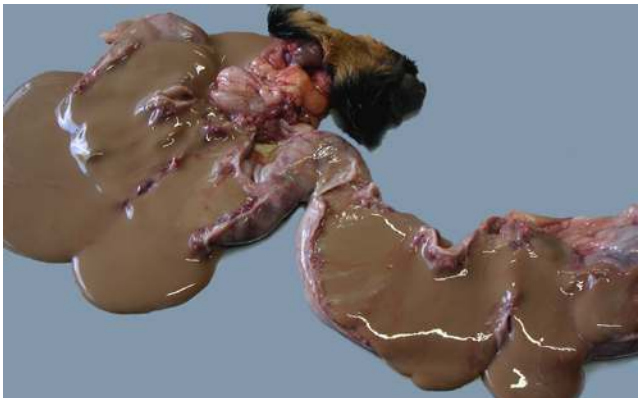

Figure 3. Female dog with pyometra. Markedly enlarged uterus containing large amounts of a brown viscous purulent exudates in a case of close-cervix pyometra (Cortesy of Dr. Silvia França Baêta).

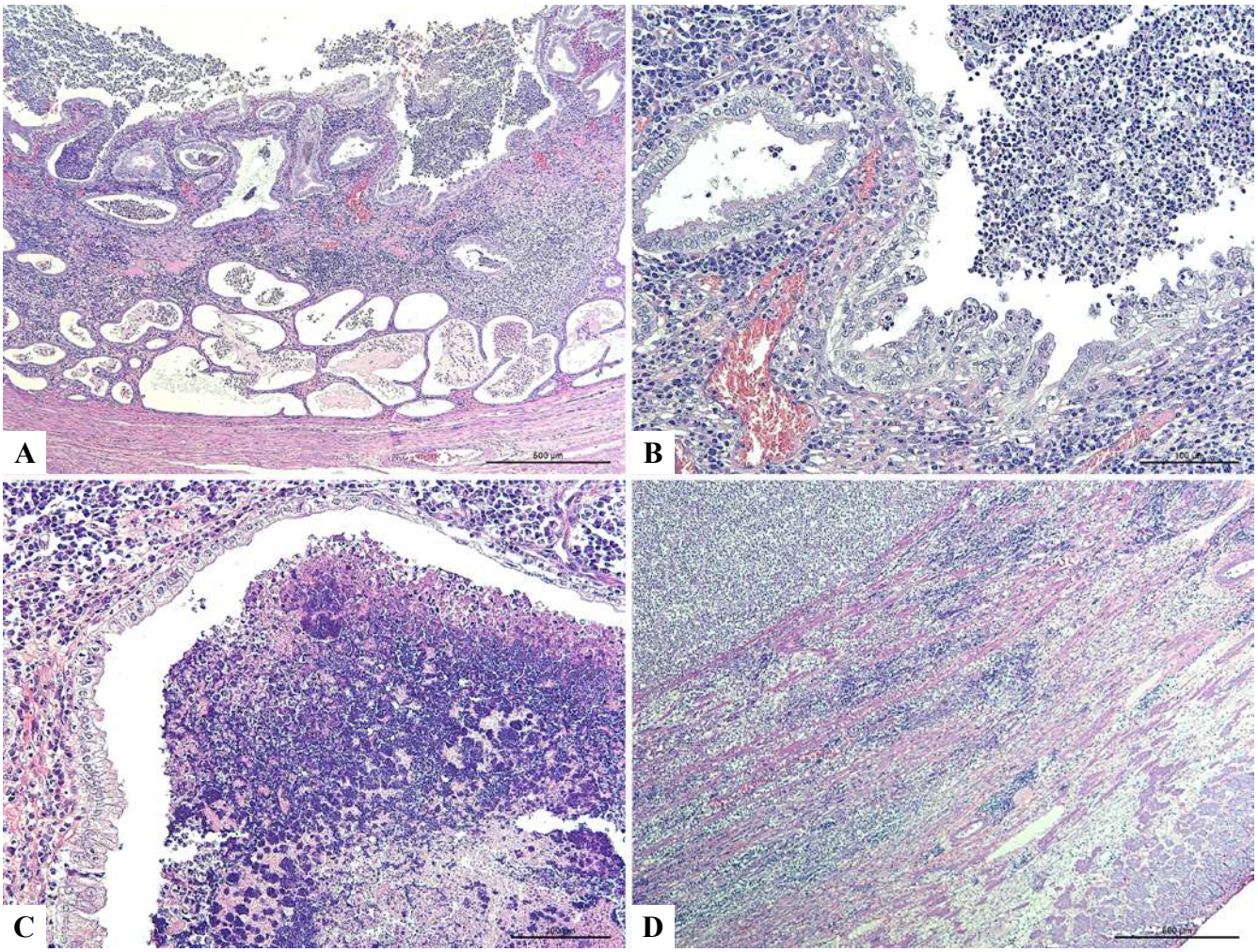

Figure 4. Female dogs with pyometra. **A.** Endometrium with diffuse severe neutrophilic and lymphoplasmacytic inflammatory infiltrate and accumulation of intraluminal neutrophils. Endometrial glands are moderately dilated. Luminal and superficial glandular endometrial epithelium with decidual reaction, characterizing pseudoplacentational hyperplasia. Hematoxylin and eosin, bar = 500 µm. **B.** Luminal endometrial hyperplasic epithelium, with papilliferous projections to the lumen and evident exocytosis of neutrophils. Endometrial epithelial cells are columnar with finally vacuolated cytoplasm, characterizing a decidual reaction. Hematoxylin and eosin, bar = 100 µm. **C.** Endometrial gland with myriad of intraluminal bacteria and eosinophilic fibrinous exudate. Hematoxylin and eosin, bar = 100 µm. **D.** Uterine wall with necrosis, ulceration and loss of the endometrial layer, and accumulation of inflammatory exudates in the uterine lumen. Myometrium with diffuse and severe neutrophilic and lymphoplasmacytic inflammatory infiltrate. Hematoxylin and eosin, bar = 500 µm.

established (39), a cause and effect relationship between these two conditions remains to be determined.

Development of CEH is thought to be initially due to estrogen stimulation followed by progesterone influence (8, 47). Interestingly, there are evidences that insulin-like grow factor 1 (IGF-1) may play a role in the development of CEH (9). Conversely, the pathogenesis of PEH is not well defined yet, but there are evidences that it may be associated with high levels of prolactin and to the clinical manifestation of pseudopregnancy (43).

Pathologic aspects of canine pyometra

There may be variable degrees of enlargement of the uterus and accumulation of intraluminal exudate in cases of pyometra. In less advanced cases or in cases of open-cervix, uterine horns are mildly to moderately enlarged and there is small to moderate amounts of intraluminal muco-purulent exudate. In advanced or close-cervix cases of pyometra, the uterus become markedly enlarged and full of large amounts of fetid purulent exudate (42) (Fig. 2). The typical purulent uterine exudate may eventually contain variable amounts of blood, giving it a brown or red color with a strong fetid odor (Fig. 3). Endometrium is usually hyperemic and thickened (42).

Grossly, prior to opening the uterine cavity, mucometra or hydrometra are quite similar to pyometra, with variable degrees of uterine enlargement. However, the uterine contents are completely different among these conditions. In both mucometra and hydrometra the intraluminal fluid is odorless, and may have a mucous appearance (35, 42).

In cases of endometrial hyperplasic lesions, associated or not with pyometra, the uterine wall is thickened, and cystic structures may be identified on the endometrial surface or on endometrial cut surfaces, and there may be variable amounts of uterine contents that may be serous, mucous or mucous-purulent, this later when associated with pyometra. When there is accumulation of large amounts of fluid in the lumen, the uterine wall and endometrium may be thinner than normal. Although CEH usually has a diffuse distribution, PEH is often segmental (31, 41, 42), but an accurate gross differentiation between these two conditions is usually not doable, especially when they are associated with pyometra.

Histologically, advanced cases of pyometra are characterized by a marked lymphoplasmacytic and neutrophilic interstitial inflammatory infiltrate, with accumulation of intraluminal neutrophils and eosinophilic amorphous fibrinous exudate (35, 39) (Fig. 4A and 4B). In some cases, it is possible to identify intralesional bacteria in hematoxylin and eosin-stained sections (Fig. 4C). There may also be extensive endometrial necrosis (Fig. 4D). Microscopically, the intraluminal fluid in cases of mucometra or hydrometra is homogeneous and lightly eosinophilic, due to its proteinaceous component, and absence of inflammatory cells neither in the tissues nor in the lumen.

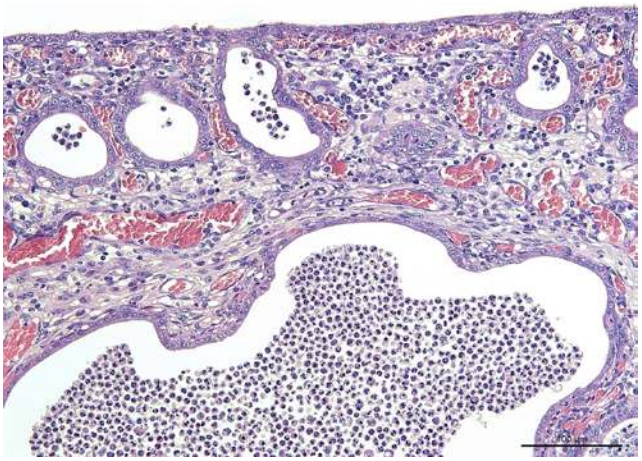

Figure 5. Female dog with pyometra. Endometrial glands cystically dilated and lined by a cuboidal to flattened epithelium, characterizing cystic endometrial hyperplasia, associated with an endometrial lymphoplasmacytic inflammatory infiltrate and intraluminal accumulation of neutrophils. Hematoxylin and eosin bar = 100 µm.

Histologically, CEH and PEH have distinct morphologic features. CEH is characterized by thickening of the endometrium with moderate to severe ectasia of endometrial glands, forming multiple cystic structures, but both endometrial luminal and glandular epithelia are single layered and cuboidal (39, 43) (Fig. 5). In cases of PEH, the endometrium is also thickened, and there may be variable degrees of endometrial glandular ectasia. However, the luminal and superficial glandular endometrial epithelium is hyperplasic, with one or multiple layers, often generating papilliferous projections to the lumen. Importantly, epithelial cells of the luminal epithelium as well as of the superficial endometrial glands are large, columnar, with a finally vacuolated cytoplasm, characterizing decidual reaction, whereas the deeper and often cystically dilated glands are lined by a single layered cuboidal to flatten epithelium without decidual reaction (39, 41, 42) (Fig. 4A). Both CEH and PEH may be associated with endometrial inflammation and pyometra.

Readers must be aware that PEH is a condition that is completely different from placentation sites (which are physiological) or the pathologic change known as subinvolution of placental sites. In healthy pregnant canine uteruses, the endometrium has areas of zonary placentation where there is attachment of the fetal placenta. Although it is not within the scope of this review to describe it in detail, different organized layers of endotheliochorial placentation are histologically recognized (15). Subinvolution of placental sites is associated with a delayed postpartum uterine involution. Grossly there are multiple areas with thickened, gray to brown and irregular endometrium corresponding to the previous placental sites. Histologically, there is hemorrhage, accumulation of necrotic debris and fibrin, fibrosis and, importantly, remaining trophoblastic cells (35).

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Comparative pathology of pyometra

Pyometra has been diagnosed in several domestic and wild mammalian species, although less frequently than in domestic dogs. Wild canids may develop pyometra and CEH similar to domestic dogs (1, 2). There are evidence of different susceptibility among wild canid species, with higher susceptibility in African painted dogs and red wolves (2).

Domestic and wild cats often develop pyometra and CEH with clinical and morphologic features that are similar those conditions in domestic dogs (28, 33). A study including Swedish insured cats demonstrated an incidence of 0.17%, and a lethality rate of 5.6% (23). Differences between cat breeds have been described, with higher incidences in Sphynx followed by Siberian, Ocicat, Korat, Siamese, Ragdoll, Maine coon, and Bengal, suggesting a genetic predisposition to pyometra (23). The lower incidence of pyometra in queens compared to bitches is due to the fact that cats have induced ovulation, which is triggered by vaginal stimulation, being less exposed to prolonged periods of progesterone stimulus on the uterus in the absence of pregnancy (44). Even when spontaneous ovulation and pseudopregnancy happen in the queen, the luteal phase has approximately 45 days, which is shorter than a normal diestrus in bitches (44, 45).

A previous study described pyometra in seven African lions (*Panthera leo*), two tigers (*P. tigris*), one liger (*lion-tiger hybrid*), and one leopard (*P. pardus*) from a sanctuary over a period of three years. Interestingly, clinical signs, including lethargy, anorexia, vomiting and vulvar discharge and abdominal ultrasonographic changes were remarkably similar to those described in bitches with pyometra. Additionally, the mean age that pyometra was diagnosed in these felines was 12 years-old, which is proportionally similar to mean age of affected female dogs (33). Therefore, preventive ovariosalpingo-hysterectomy should be considered in captive wild felids, when breeding and reproduction is not desired (33). We had an unpublished case of pyometra in a captive female African lion (*Panthera leo*) that was successfully treated by surgery (Fig. 6).

Pyometra has also been reported in captive collared peccary (*Tayassu tajacu*) (4), European hedgehog (*Erinaceus europaeus*) (16), agouti (*Dasyprocta aguti Linnaeus*) (3) and spotted seal (*Phoca largha*) (25). There are reports of pyometra in guinea pigs and chinchillas (30), and in rodents and lagomorphs, including mice and rats, in which it is associated with *Klebsiella oxytoca* and *Pasteurella multocida* systemic infections, respectively (36, 37).

Although other domestic species including mares, cows, does, and ewes can develop pyometra, it is not associated with endometrial hyperplasic changes. Pyometra in cows is highly frequent, usually consequence of a postpartum or postcoital infections (35). In the mare pyometra is a consequence of vaginitis and cervicitis, frequently associated to *Streptococcus zooepidermicus* (35).

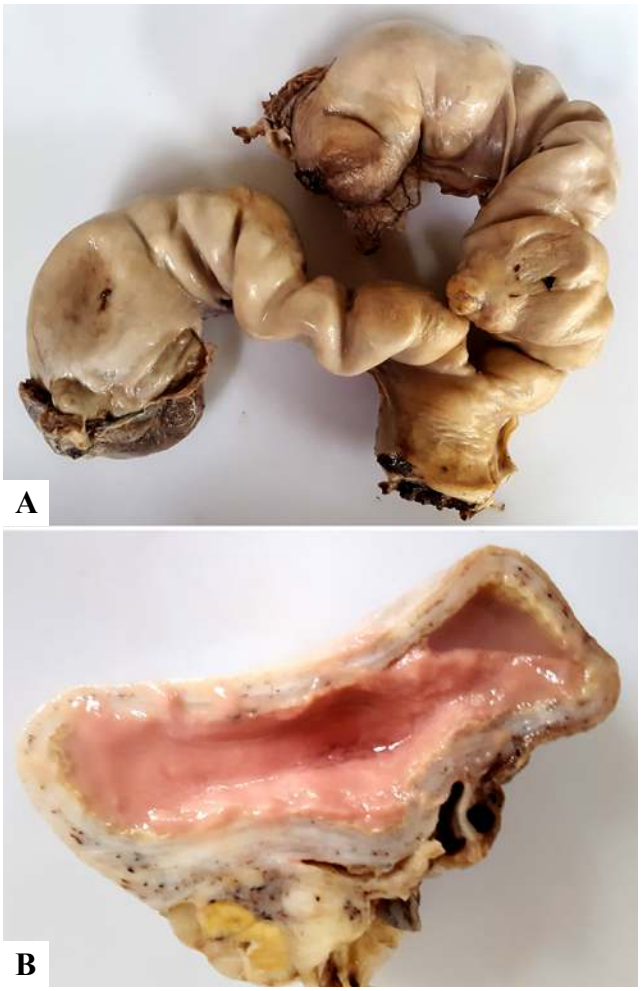

Figure 6. Female African lion (*Panthera leo*). Uterus. **A**. Formalin-fixed uterine horns markedly enlarged due to intraluminal accumulation of purulent exudates in a case of pyometra. **B**. Cross section of a uterine horn with an irregular endometrium, and the lumen filled with large amounts of exudate.

Concluding remarks and perspectives

Canine pyometra is a common and life-threatening disease of intact female dogs, which is often associated with systemic complications, with a poor prognosis if untreated. Multiple aspects of this disease remain unclear including genetic predisposing factors, innate endometrial immune response, and a thorough bacteriologic characterization of isolates. Therefore, future studies may lead to a better understanding of this disease, which may provide the basis for the development of better preventive protocols.

Absence of significant association between CEH and pyometra, but a significant association with PEH and pyometra has been recently described (39). However, the pathogenesis of PEH, and a possible cause and effect relationship of this condition with canine pyometra remains to be investigated. Another important aspect to be clarified in future studies, is whether PEH is a common change and associated with pyometra in other domestic and wild species.

Although the concept of "CEH – pyometra complex" was soundly based on the seminal experimental work by Dow (11, 12), it is now clear that pyometra is more often associated with PEH than with CEH (39). Therefore, we strongly recommend that the diagnostic terms "pyometra", "pseudoplacentational endometrial hyperplasia", and "cystic endometrial hyperplasia" should be employed separately and referring to specific uterine pathologic changes. Furthermore, the concept of "CEH – pyometra complex" has become obsolete under the light of recent studies (39, 43) so it should no longer be employed as a synonymous of pyometra.

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