

Cystic endometrial hyperplasia, pseudo-placentational endometrial hyperplasia, and other cystic conditions of the canine and feline uterus

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Abstract

Cystic lesions in the uteri of bitches and queens arise 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). Of these, “cystic endometrial hyperplasia (CEH)” is the most common and is frequently associated with pyometra. A second form of endometrial hyperplasia occurs in the bitch; although it was first described over 100 y ago, it is not widely recognized by clinicians or diagnostic pathologists. In this form, the endometrium proliferates in a highly organized manner, remodeling the uterine lining to closely resemble the histology of the endometrium at placentation sites in normal pregnancy. Although this lesion is very different from CEH, it is quite easy to induce in dogs during the luteal phase of their cycles and has been perhaps inappropriately proposed as modeling CEH. This lesion has been referred variously as “deciduoma”, endometrial hyperplasia in pseudocyesis, and “maternal placental-like endometrial hyperplasia”. An alternative name is suggested that is descriptive and draws attention to the difference between this lesion and CEH; the term pseudo-placentational endometrial hyperplasia (PEH) is proposed. The histopathology and pathogenesis of CEH and PEH are discussed. The objectives of this paper are to review the pathophysiology of cystic lesions of canine uterus, to demonstrate these using subgross photomicrographs taken from natural cases, and to present key diagnostic features of each.

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1. Introduction

1.1. Cystic conditions of the canine and feline uterus

Cysts arising from the wall of the canine uterus can be divided into those that involve the endometrium (by far the most common and clinically important) and

those that arise within the myometrium or from the serosal surface of the uterus. Cysts that develop from the endometrium (generally referred to as cystic endometrial hyperplasia or CEH) vary greatly in size, number, distribution, histomorphology, and clinical relevance. Cystic endometrial hyperplasia is an important common lesion that can progress to pyometra [1–3]. The pathogenesis of endometrial hyperplasia, associated cyst development, and/or progression in some cases to pyometra has been of keen interest and has been the subject of many experimental [4–29] and clinical studies. The latter have included assessment of methods for accurate clinical diagnosis [30,31] and treatment

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response to various protocols [32–36]. A specific form of canine endometrial hyperplasia was first observed by researchers who, while conducting surgical experiments on canine uteri [37,38], noted marked endometrial proliferative responses at the surgical sites. The pathogenesis of these lesions will be contrasted to those of the more common cystic changes of individual endometrial glands.

Many of the less common cysts found in the canine uterus are incidental findings, but these can be dramatic in appearance and can nearly always be diagnosed based on their location and other features.

The objectives of this paper are to review cystic conditions involving the uterus of the bitch, to present examples of the most common of these, and to discuss their pathogenesis and diagnosis.

2. Methods

The literature relating to the patho-physiology of cystic lesions in the bitch and queen was reviewed. Cases diagnosed with common cystic uterine lesions were identified from either the senior author's reproductive pathology archives or the files of the Section of Anatomic Pathology of the Animal Health Diagnostic Center at Cornell University. Glass slides that exemplified key morphologic features of the cystic uterine lesions were chosen. Demonstration of size, distribution, and many other important morphologic features could easily be appreciated by examination of tissue sections on glass slides prepared for histopathology. For this paper, "subgross" photographs were prepared using a digitizing slide scanner. Photomicrographs were also taken for demonstration of other key features. (Note that colour images of the photographs are available for review in the on-line version of the manuscript.)

Because of their importance, cystic conditions involving the endometrium will be presented first, followed by a section (Section 6) that addresses other less common uterine cystic lesions.

3. Cystic conditions of the endometrium

Endometrial cysts of the queen and bitch generally arise from endometrial glandular epithelium (Figs. 1 and 2), but in at least one subset (discussed in Section 5), endometrial cysts also develop from thin villous folds covered by luminal epithelium. Hyperplastic endometria frequently become inflamed and infected (or vice versa), and the condition may progress to development of pyometra, with possible life-threatening systemic illness.

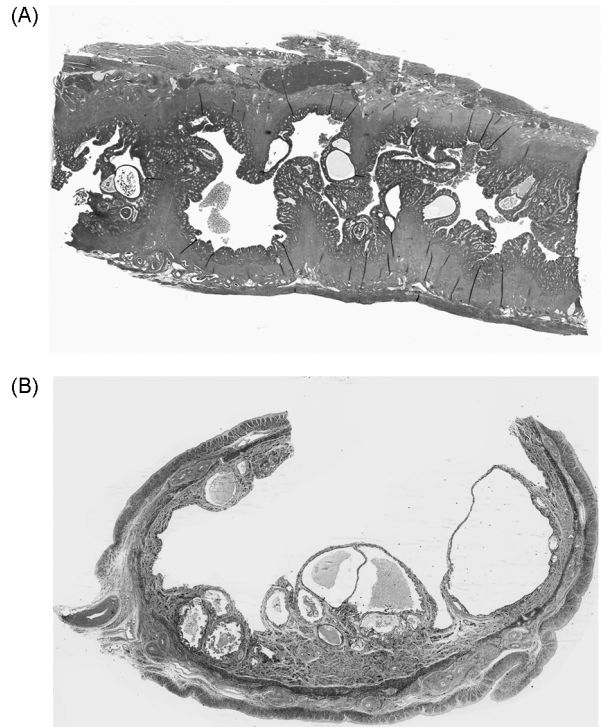


Fig. 1. Subgross photographs of two cases of canine CEH. (A) Longitudinal section of a uterine horn of a bitch with CEH. Arrows indicate multiple small similarly sized glandular cysts that were distributed throughout both uterine horns and uterine body. (B) Cross-section of a uterine horn of a different bitch with severe CEH, showing multiple cysts of variable size. Individual cysts can be 1–2 cm in diameter. In these two examples, there is no inflammation of uterine tissues.

3.1. Historical perspective

In the late 1950's, Dr. C. Dow in Scotland published the results of a large study that included summation of the histopathology of 172 canine uteri that had either cystic glandular hyperplasia or pyometra [14]. It was known before this time that some bitches have cystic endometrial glandular hyperplasia associated with co-existing inflammation, and others do not. Prior to the publication of his seminal paper, it was known that pyometra was a "post-oestral syndrome" of the adult bitch [14], but Dow's study provided a substantial amount of then new data that confirmed and expanded on these earlier observations. Dow was the first to propose the term "cystic hyperplasia-pyometra complex" which has now become the "cystic endometrial hyperplasia/pyometra complex".

Dow's data documented that endometrial cystic change, with or without inflammatory cellular infiltrates, most commonly occurred in older dogs (Fig. 2). The mean age for dogs with CEH and no inflammation

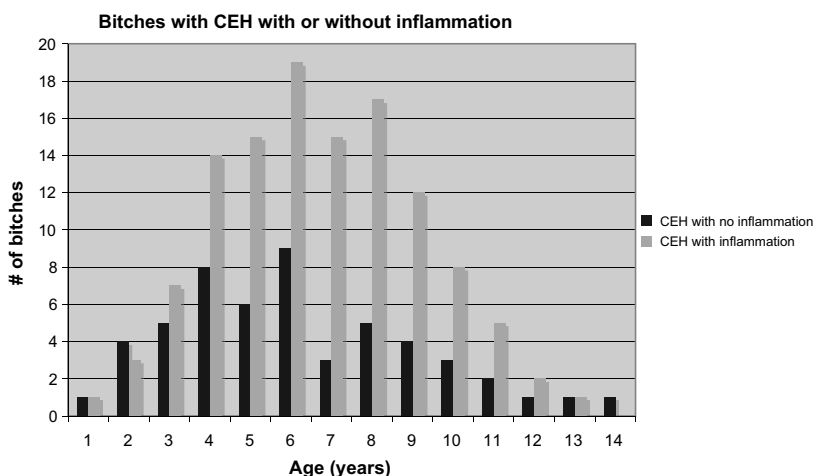


Fig. 2. Data initially published in 1958 by Dr. C. Dow [14] and plotted here as a histogram showing the ages of bitches with CEH and the presence or absence of associated endometritis. The mean age of bitches with CEH without endometrial inflammation was 8.1 ± 3.1 y, compared to 7.6 ± 2.2 y of age for bitches with CEH and primarily plasmacytic inflammation and 8.3 ± 2.3 y for bitches with primarily neutrophilic inflammation. (Data from the latter two groups are combined in the graph as bitches with CEH and either acute or chronic inflammation.).

was 8.1 ± 3.1 y, dogs with primarily neutrophilic inflammation were 8.3 ± 2.3 y old, and dogs with CEH and predominantly plasma cell inflammatory infiltrates were 7.6 ± 2.2 y.

As these and other data published more recently show, many bitches with cystic endometrial changes do not always have associated endometrial inflammation (Figs. 1 and 3A). Although CEH can be an incidental finding, if the cystic lesions are extensive and large (Fig. 3A) they likely could interfere with distribution of embryos along the uterine horns or inhibit placental attachment and development.

Dow's work also provided data on the relationship among stage of cycle, CEH, and the presence of endometritis.

3.1.1. CEH: a post-estrous luteal phase disease

Dow's pioneering work also provided data that firmly established that cystic endometrial hyperplasia and associated endometritis occurred primarily in bitches that had gone through estrus and were in the luteal phase of their reproductive cycles (Fig. 4) [14]. Dow's data revealed that acute inflammation developed in dogs in the earlier luteal phase and that more chronic inflammation was found in dogs with CEH later in the luteal period. He was also the first to observe that pregnancy has a protective effect against development of pyometra, reporting that the number of nulliparous bitches with pyometra was approximately 10-fold greater than in multiparous bitches.

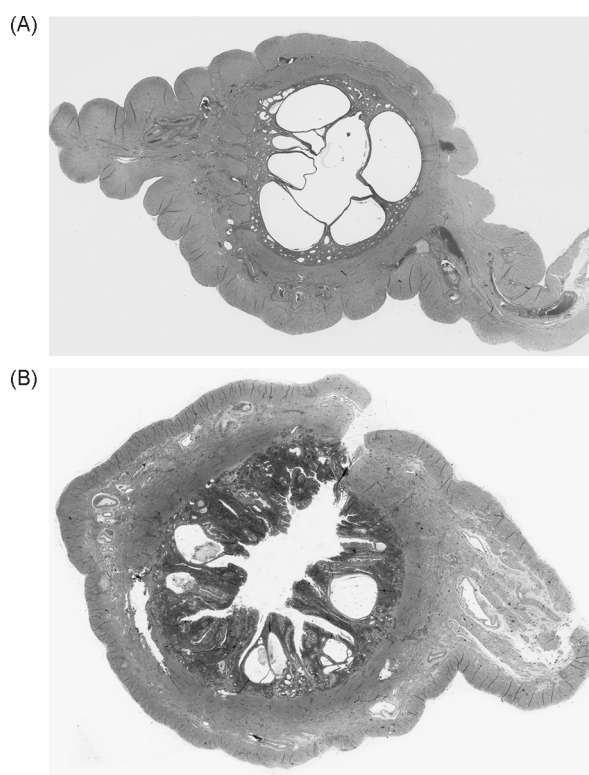


Fig. 3. Comparison of CEH with and without inflammation. (A) Cross-section of a canine uterine horn with multiple large endometrial cysts without associated inflammatory cellular infiltration. Note the encroachment on the uterine lumen. (B) Moderately severe canine CEH with intense plasmacytic cellular infiltrate within the endometrium.

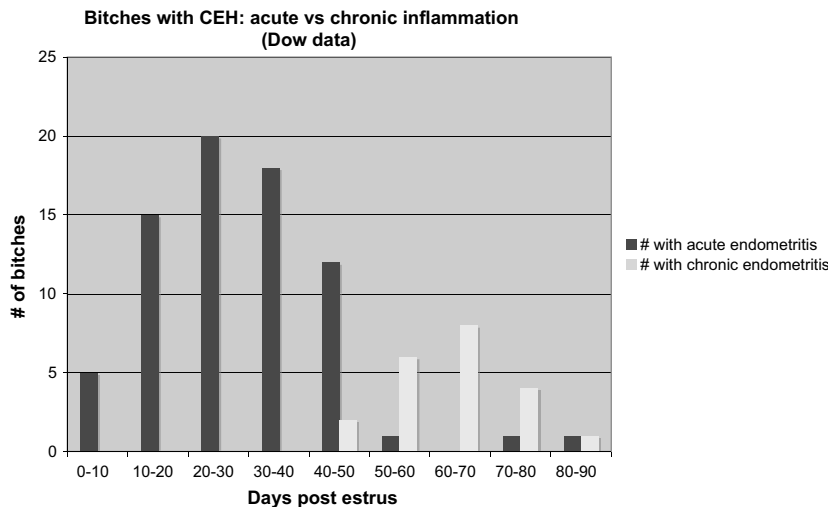


Fig. 4. Histogram of data initially published in 1958 by Dr. C. Dow [14], showing the number of bitches with either acute or chronic inflammation associated with their CEH in relation to the stage of their estrus cycle. Acute inflammation was much more commonly found within the first 40 d after estrus (30 ± 13 d). Conversely, mostly plasmacytic inflammation was found in uteri from bitches in later stages of the luteal phase of their estrous cycles.

3.2. CEH/pyometra complex

Endometrial hyperplasia is associated with uterine bacterial infection in bitches and queens (Figs. 5 and 6). Information is now available on the relative frequency of pyometra in a large sample of the general population of dogs from a report from Sweden, where very accurate data are available [39]. Approximately 30% of all dogs in Sweden are covered by animal health insurance, thus providing a wealth of canine health-related data [39]. In their study published in 2001, Egenvall et al. [39] reviewed animal insurance records from over 200,000 Swedish dogs. Over a 2-y interval, claims were submitted for pyometra in 1803 bitches for 1995 and 1754 bitches in 1996. For bitches that were <10 y old, they reported a “crude 12-mo risk” of pyometra of 2.0 and 1.9% for the 2-y included in the study, respectively. Their analysis showed that “23–24% of the bitches in the databases will have experienced pyometra by 10 y of age” [39].

In another study published the same year, Fukuda investigated the incidence of pyometra that developed in colony-reared beagles ($n = 165$) that were studied over a 12-y interval [40]. He found that 15.2% developed pyometra, which was detected at an average age of 9.36 ± 0.38 y [40].

3.3. Experimental models: pathophysiology of canine endometrial hyperplasia and pyometra

Although a great deal of information has been gained from studies of spontaneous cases of canine endome-

trial hyperplasia, further delineation of key factors that play a role its development and progression have come from a variety of experimental models.

It has generally been assumed that the pathogenesis of the CEH/pyometra syndrome involves the progression of events starting with development of endometrial hyperplasia, with or without cyst formation, which somehow stimulates a local inflammatory reaction. In turn, the hyperplastic endometrium causes secretions to accumulate, followed by the establishment of a bacterial infection. Infection within the endometrial and uterine lumen would then result in accumulation of exudate in the uterine lumen (pyometra).

An alternative hypothesis has been considered for some time, i.e. that low-grade uterine infection is partially responsible for some of the endometrial proliferation that occurs early in the pathogenesis of CEH/pyometra complex. Factors responsible for the initial plasmacytic inflammation (Fig. 3B), commonly found without accompanying neutrophilic inflammation, remains unclear. Extensive endometrial interstitial infiltration by plasma cells and lymphocytes without accompanying neutrophils is a common finding. A possible explanation for this unusual response is that the lympho-plasmacytic infiltrates represent a cellular inflammatory reaction to low-grade, subclinical, chronic bacterial infections that develop during proestrus or estrus when cervical patency allows ascending infection to occur. The possible role of bacteria that enter the uterus during estrus was proposed in the 1960's [37]; Noakes et al. further suggested that the

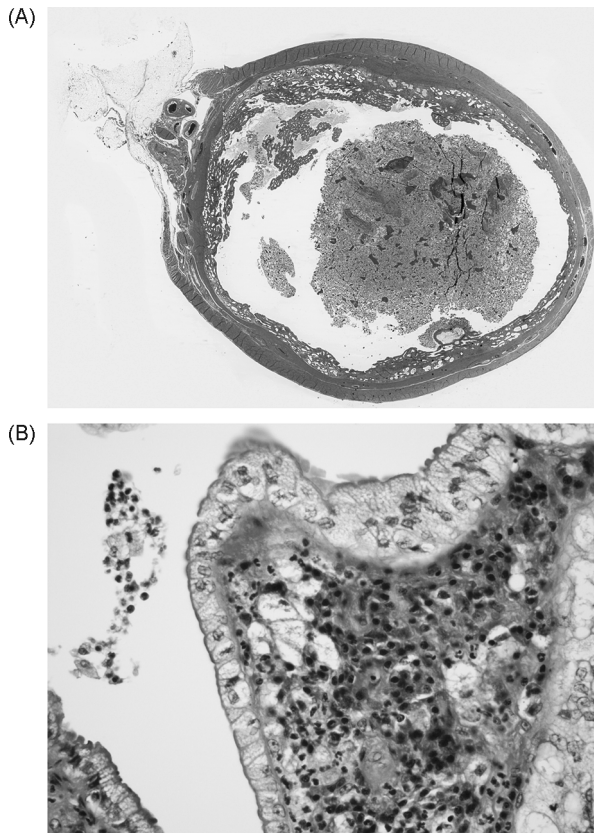


Fig. 5. (A) Cross-section of a canine uterus with accumulation of purulent exudate within the uterine lumen (pyometra). (B) Pyometra and subacute endometritis. Photomicrograph from a different case, showing markedly hyperplastic uterine luminal epithelium and intense neutrophilic and plasmacytic cellular interstitial infiltrate in the endometrium. Sloughed cells and neutrophils are free within the lumen on the left side of the image.

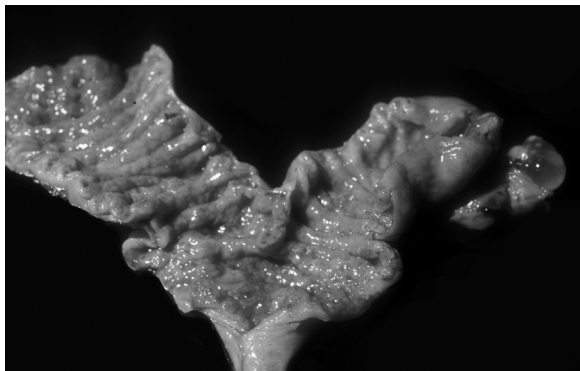


Fig. 6. Opened uterus from a cat with pyometra, showing marked endometrial hyperplasia and hypertrophy (purulent exudates have been removed). Large numbers of small endometrial cysts were evenly scattered throughout the endometrium (as demonstrated in the subgross photograph of the canine uterus in Fig. 1A).

mechanisms through which bacteria affect the endometrium might be mediated directly through bacterial toxins, or indirectly through release of inflammatory mediators [2].

The pathogenesis of the CEH/pyometra syndrome likely involves changes within the endometrium and specific characteristics of invading bacteria. It has been shown that matrix metalloproteinases, known to have a role in endometrial remodeling in humans, are not elevated in canine CEH, but are elevated in CEH with pyometra [8]. Additionally, there is a decrease in the lectin staining patterns of the glycocalyx in affected glandular epithelium in bitches with CEH/pyometra compared to normal controls [17]. Furthermore, IGF-1, a known potent stimulator of endometrial proliferation, is present in markedly increased amounts, as detected by immunohistochemistry [11]. It was recently reported that *Escherichia coli* isolates recovered from spontaneous cases of pyometra are capable of causing various types of lesions within the endometrium, possibly related to toxic factors produced by them [12].

3.4. Reactivity of the canine endometrium to a broad range of stimuli

It has been clear for some time that during the luteal phase of the cycle, the canine endometrium is very sensitive to mechanical stimulation or to stimulation by the presence of foreign material placed within the uterine lumen. As early as 1914, endometrial proliferation was observed at uterine surgical sites during experiment studies by Krainz [38]. Segmental areas of endometrial hyperplasia were also found by Hadley in bitches he had biopsied [37].

Hyperplastic changes have been induced by experimental manipulation of the uterine lumen of bitches. (Similar lesions are not reported for the cat.) In a classic series of papers, Nomura and co-workers demonstrated the sensitive and highly responsive nature of the luteal-phase endometrium, through a series of experimental studies during which a variety of material was surgically placed within the uterine lumen. Others have used some of these protocols to study the pathogenesis of endometrial hyperplasia. Materials placed within the uterine lumen include silk suture [20,21,25–27], olive oil [22], bouillon and barium [24], allografts and autographs of uterine tissue [23], and bacteria (*E. coli*) [4,16,28,29]. Nomura also showed that the dog, like rodents and primates, develops endometrial proliferation following minor mechanical irritation [22] and this technique has been used by others [10].

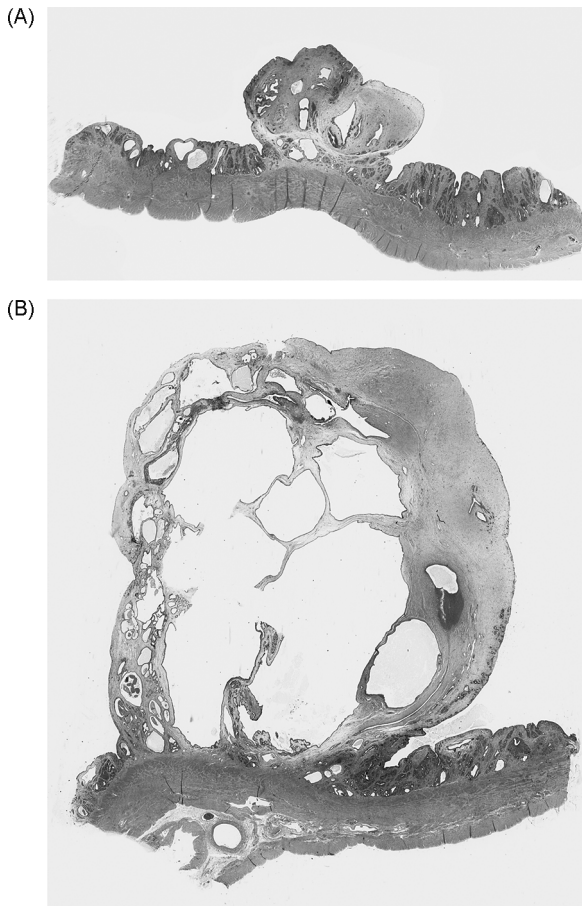


Fig. 7. Sections of the uterine wall of two bitches with endometrial polyps associated with CEH. (A) A small endometrial polyp and multiple small endometrial cysts within the endometrium of a dog without evidence of pyometra or significant endometritis. (B) A large endometrial polyp that compromised the uterine lumen.

3.5. Role of hormones and hormone receptors

Models of endometrial hyperplasia have been proposed that involve either administration of hormones [4,6,7,33] or compounds that block hormones [33,34,36]. Progesterone concentrations in bitches with CEH are not abnormally high [37], but administration of progestagens, especially after estrogen priming, predispose to the CEH/pyometra syndrome [5–7]. Exogenous administration of progesterone in ovariectomized bitches depressed steroid hormone receptors, but there was no long-term down regulation [9]. Although estrogen and progesterone receptors may be modified by experimental administration of steroid hormones, it has been suggested that changes in steroid hormone receptors are not involved in the pathogenesis of the CEH/pyometra syndrome [2].

4. Other endometrial lesions related to CEH: endometrial polyps

Small aggregates of cystic endometrial glands sometimes stimulate deposition of interstitial fibrous connective tissue that can expand and protrude to form endometrial polyps. Bitches and queens may have only one or several endometrial polyps, which are frequently small and of little consequence (Fig. 7A). Occasionally larger polyps develop that can compromise the uterine lumen (Fig. 7B).

5. Endometrial hyperplasia resembling maternal placental tissues (pseudo-placentational endometrial hyperplasia; PEH)

A second form of endometrial hyperplasia was initially reported nearly 100 y ago [38], and although it is described in standard textbooks [41,42], it is not widely recognized by clinicians or diagnostic pathologists. As with CEH, it occurs primarily during the luteal phase of the cycle when the endometrium is highly sensitive, as demonstrated in a series of papers published by Dr. Kochi Nomura and colleagues from the University of Osaka Prefecture [18–28].

Unlike that seen in classical CEH, the endometrium in this form of endometrial hyperplasia responds to stimuli with a highly organized proliferative remodeling that is very similar to the normal histology of the endometrium at placentation sites in normal pregnancy (Figs. 8 and 9).

This lesion is very different from CEH. It has been referred variously as “deciduoma” [20] (the name, however, suggest that this is a neoplastic lesion), endometrial hyperplasia in pseudocyesis [41], and “maternal placental-like endometrial hyperplasia” [43]. The authors suggest an alternative name that is descriptive and draws attention to the difference between it and CEH; the term pseudo-placentational endometrial hyperplasia (PEH) is proposed.

6. Cysts that arise from uterine tissues other than the endometrium

These cysts can be congenital (i.e., cystic remnants of the male embryonic ductal system) developmental (adenomyosis within the myometrium), or acquired (serosal inclusion cysts that develop from the peritoneum lining the surface of the uterus). An embryonic vesicle could be confused as being a cystic uterine lesion and pregnancy and should always be considered. Most of these lesions can be identified based on

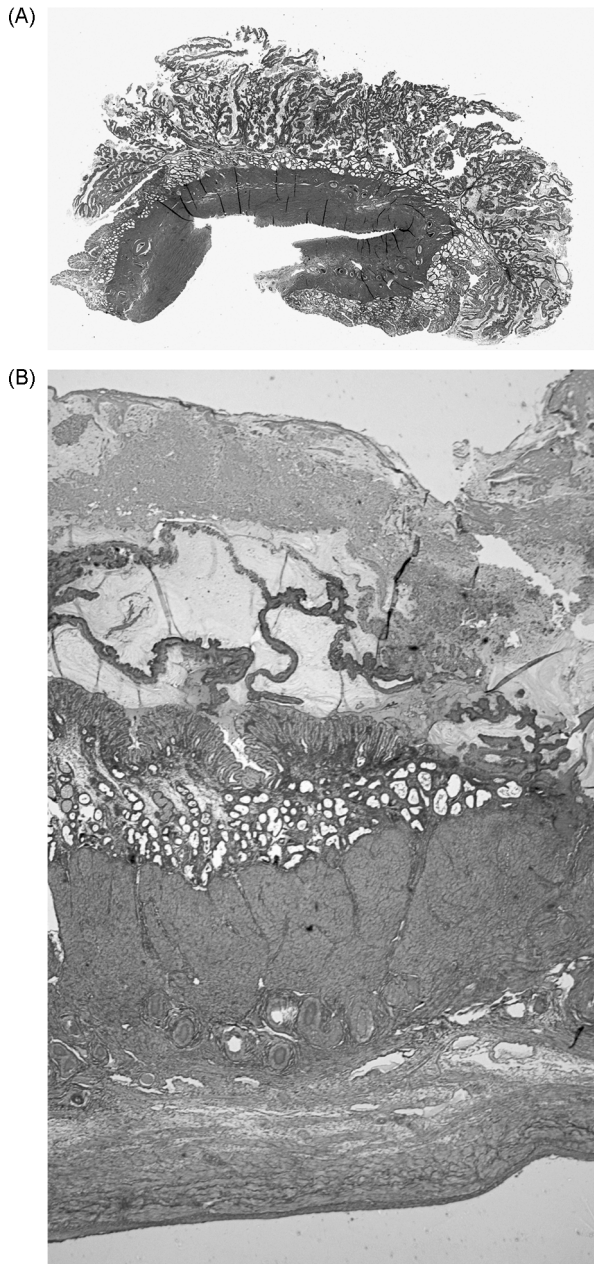


Fig. 8. A. Marked segmental endometrial hyperplasia that morphologically resembles sections of uterine wall beneath normal placenta attachment areas. This specific form of endometrial hyperplasia has been referred to as “deciduoma”, segmental endometrial hyperplasia, or endometrial hyperplasia of pseudo-pregnancy. As none of these terms captures the nature of this relatively common lesion, the term pseudo-placentational endometrial hyperplasia (PEH) is proposed. The endometrial remodeling produces three layers, as demonstrated in 8B. The uterine lumen (top) is lined by long villous folds extending from the endometrial surface and contains accumulations of endometrial secretions. The middle more dense layer is covered by a folded layer of hyperplastic and hypertrophied endometrial epithelial cells overlying a more dense band of connective tissue. The third and outermost layer of the endometrium (closest to the myometrium at the

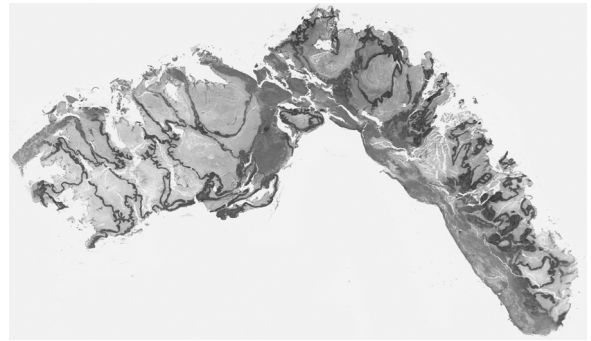


Fig. 9. Multiple cystic spaces filled with mucous secretions along the surface of the endometrium associated with pseudo-pregnancy endometrial hyperplasia. In this case, the spaces between the long thin extensions projecting from the endometrial surface have entrapped dense mucoid secretions.

location, number and size. There are no data available regarding their relative incidence.

6.1. Cystic remnants of mesonephric ducts

Sexual differentiation during embryonic development involves development of two paired ductal systems (male – mesonephric; female – paramesonephric). Uterine tubes, the uterine horns and body, cervix, and cranial vagina develop from the female (paramesonephric) ductal system, but remnants of the embryonic male ductal system can be found along the uterine horns or body as either single smooth muscle-lined cysts of variable size (usually <1 cm) near the attachment of the broad ligament (mesometrium) or, in cases of intersex animals, as tubular structures also running longitudinally in the mesometrial tissues (Fig. 10).

6.2. Adenomyosis

Adenomyosis is the presence of endometrial tissue ectopically within the myometrial (muscle) layers of the uterine wall. They may be small and have the appearance of an endometrial gland, or they may be multiple, or larger with more proliferative endometrial epithelial cell lining. As secretory products accumulate and pressure increases, the lining may undergo atrophy and in some cases disappear entirely, leaving a cyst within the myometrium that is lined by connective

bottom of the photomicrograph) contains many uniformly distended endometrial glands. Contrast these images of PEH to those of CEH in Figs. 1 and 3.

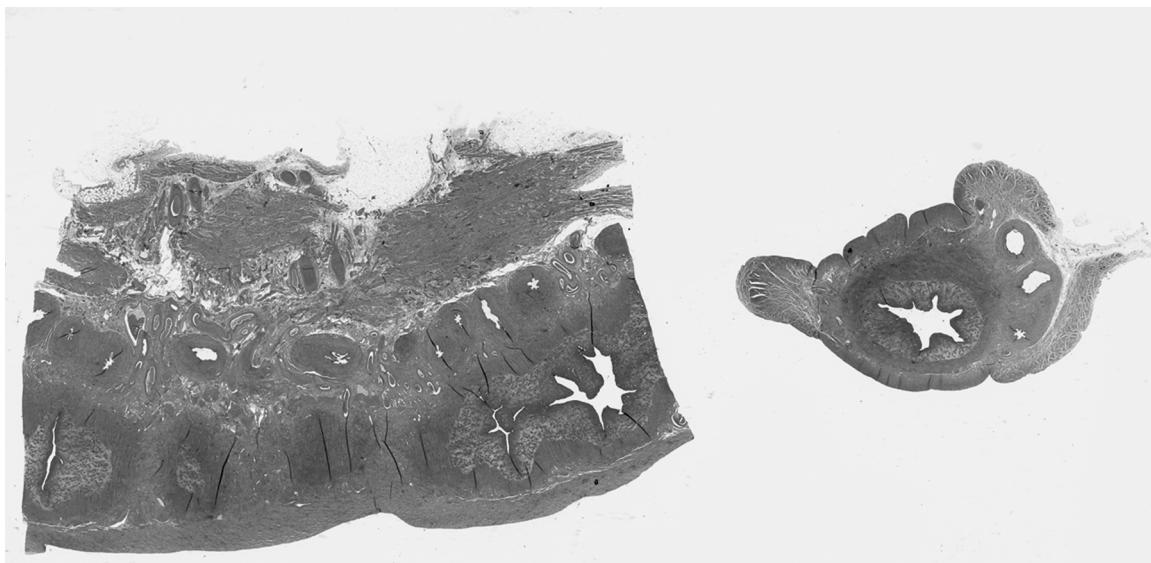


Fig. 10. Longitudinal and cross-sections of a canine uterus containing segments of a mesonephric duct in their wall. These or single cystic remnants of the mesonephric ducts are only found near the attachment of the broad ligament.

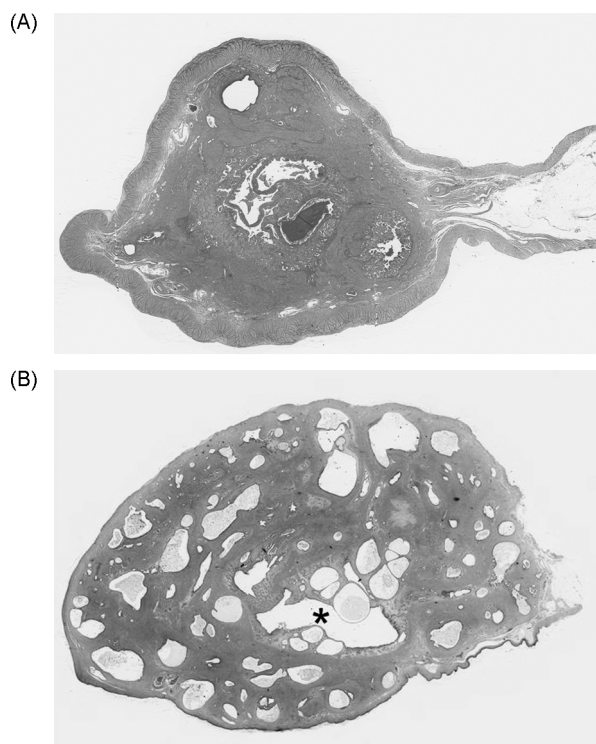


Fig. 11. (A) Adenomyosis is a relatively common lesion and can be found as single small ectopic endometrial glandular tissue embedded within the endometrium, or larger cystic structures. (B) An extreme case of canine uterine adenomyosis producing a "Swiss cheese" appearance to the uterine wall. The uterine lumen is labeled (*).

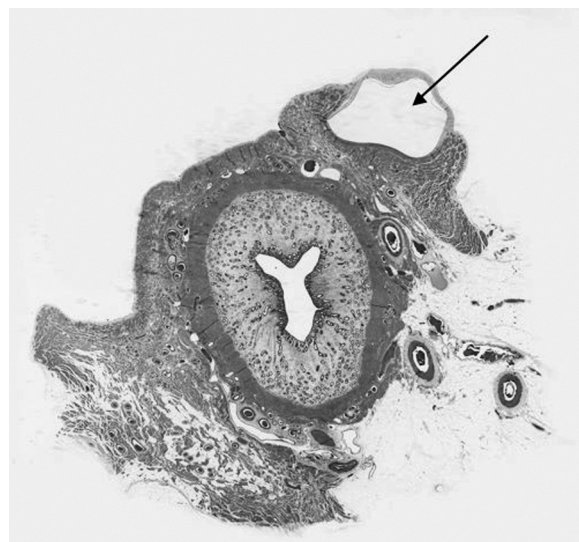


Fig. 12. Serosal inclusions cyst (lumen indicated by the arrow) protruding from the serosal surface of a uterine horn cut in cross section. These arise in middle-age or older bitches from areas of mild peritoneal reactivity that leads to entrapment of peritoneal tissues with subsequent proliferation and secretion. Serosal inclusion cysts are very thinned walled, may be single or multiple, and contain clear non-viscous fluid.



Fig. 13. “Cystic” segmental distention of a uterine horn at a pregnancy implantation site. The differential diagnosis for cystic conditions of the uterus must always include embryonic vesicles.

tissue only. In extreme cases, this can produce a “Swiss cheese” pattern in the uterine wall (Fig. 11).

6.3. Serosal inclusion cysts

Serosal inclusion cysts that develop on the surface of the uterus start as areas of mild peritoneal reactivity which leads to entrapment of small pieces of serosa. Subsequent secretion from this serosa produce very thin-walled cysts that protrude from the surface (Fig. 12). They may be single or multiple, and frequently occur in clusters on any aspect of the peritoneal covering of the uterine horns or body. They contain clear non-viscous fluid. These are commonly seen in bitches following Cesarean section where the uterus has been handled extensively.

6.4. Pregnancy

Embryonic vesicles (Fig. 13) could be mistaken for a uterine cystic lesion, especially if only one or a few were present. Pregnancy must always be ruled out when considering fluid filled uterine “lesions”.

7. Conclusions

Cystic lesions of the canine and feline endometrium are common and can be readily identified based on their location, distribution and morphology, as demonstrated in the subgross photographs presented in this paper.

Proliferative changes involving the endometrium can result in cyst formation. Selecting appropriate descriptive terms to describe these conditions can be difficult, frustrating, and potentially confusing. This is especially true of the endometrium, which changes dramatically during the normal estrous cycle and even more

markedly at placentation sites in pregnancy. Endometrial tissue changes judged to be “exuberant” become “lesions” when they produce detrimental effects on reproduction.

Clearly there are two forms of endometrial hyperplasia in the bitch. Both are pathologic, but they represent different types of reactions, with one involving cystic distention of parts of endometrial glands (CEH), the other, (PEH) representing a luteal phase, highly organized limited transient adaptive response that partially duplicates the maternal endometrial proliferative remodeling associated with placentation. These two lesions differ dramatically in their appearance, pathogenesis and clinical relevance, and should be distinguished by pathologists, clinicians, and those that would develop valid experimental models of these common and important uterine conditions. The authors propose the use of the term pseudo-placentational endometrial hyperplasia to help distinguish it from CEH.

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